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TOXIC HAZARDS RESEARCH UNIT ANNUAL TECHNICAL REPORT: 1968

J. D. MacEWEN

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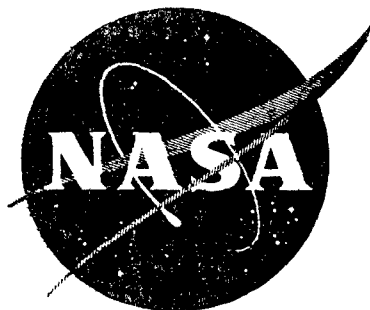
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OCTOBER 1968

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences—National Research Council; the regulations and standards prepared by the Department of Agriculture; and Public Law 89-544, "Laboratory Animal Welfare Act," August 24, 1967.

The voluntary informed consent of the subjects used in this research was obtained as required by Air Force Regulation 169-8.

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**TOXIC HAZARDS RESEARCH UNIT
ANNUAL TECHNICAL REPORT: 1968**

J. D. MacEWEN

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FOREWORD

This is the fourth annual report of activities of the Toxic Hazards Research Unit Laboratory and concerns work performed by SysTeMed Corporation on behalf of the Air Force under Contract No. F33615-67-C-1025. This contract originally held by Aerojet-General Corporation was assumed by SysTeMed Corporation on 1 December 1968. There was no change in the management or personnel of the THRU Laboratory related to the change in companies. This report describes the accomplishments of the THRU from September 1967 through May 1968.

The contract for operation of the laboratory was initiated in 1963 under Project 6302 "Toxic Hazards of Propellants and Materials," and Task No. 630201, "Toxicology." K. C. Back, Ph.D., Chief of the Toxicology Branch, is the technical contract monitor for the 6570th Aerospace Medical Research Laboratories.

E. J. Fairchild II, Ph.D. of Aerojet-General Corporation, served as principal investigator and Laboratory Director until October 1967, at which time this responsibility was reassumed by J. D. MacEwen, Ph.D. Acknowledgement is made to C. E. Johnson, C. C. Haun, G. L. Fogle, G. F. Egan and J. H. Archibald for their contributions and assistance in the preparation of this report. The National Aeronautics and Space Administration provided support for the Apollo Materials Toxicity Screening Program.

This report is designated as SysTeMed Corporation Report No. W-68001.

This technical report has been reviewed and is approved.

WAYNE H. McCANDLESS
Technical Director
Biomedical Laboratory
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ABSTRACT

The activities of the Toxic Hazards Research Unit (THRU) for the period of September 1967 through May 1968 are reviewed in this report. The experimental research program was partially curtailed during the first half of this period while major modifications to the Thomas Domes of the Altitude Facility were being completed. The dome modifications, primarily for improved fire safety protection, were required to be complete before experimentation in oxygen enriched environments could be resumed. Additional facilities for toxicity screening of space cabin materials were placed in service and the evaluation of materials has been continued with little evidence of toxicity exhibited by their gas-off products. One cabin material, carboxy nitroso rubber (CNR), did exhibit toxic manifestations and its acute toxic effects were investigated in depth. The CNR pyrolysis products formed at 300 C were found to be highly toxic and any human exposure to these products should be guarded against. Acute toxicity experiments on monomethylhydrazine and nitrogen trifluoride, including MMH emergency tolerance limits studies were conducted in the Ambient Facilities of the THRU. Investigations on the use of sham exposed dome controls and techniques for determining organ to body weight ratios are reported.

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SECTION I

INTRODUCTION

The Toxic Hazards Research Unit (THRU) provides toxicologic investigations of potentially hazardous materials to the Air Force. These investigations, conducted by SysMed Corporation personnel, are designed to characterize the acute or chronic toxic effects of materials to which military or civilian personnel may be accidentally or unavoidably exposed. Considerable research is also conducted to define the toxicological hazards of space flight and to establish safe environmental standards for such flights. The toxicologic research of manned space flight problems is concerned with defining the risk of breathing trace air contaminants resulting from outgassing of agents incorporated in cabin construction materials and of chemicals used for propulsion and life support systems. This research is conducted on several species of laboratory animals under conditions which simulate space flight as closely as possible, with the exception of radiation and weightlessness.

The research operations of the THRU, conducted by SysMed Corporation personnel, are supported by the Veterinary Medicine Division and the Toxic Hazards Division of the Aerospace Medical Research Laboratories. These support services include veterinary medical care, procurement of laboratory animals, and both clinical and anatomical pathology examinations of animal tissues.

The continuing research programs of the THRU involving the interdisciplinary approach of the inhalation toxicology team (analytical chemistry, medical technology, pathology, engineering and biological sciences) are conducted in a group of laboratories surrounding the animal exposure facilities. These facilities are three types of animal exposure chambers, each performing a separate specialized function. Preconditioning chambers are used to prepare and stabilize animals in a controlled environment. Rochester and Longley chambers are used for exposing animals to atmospheric contaminants under ambient conditions of pressure and air composition. A group of four specially designed altitude chambers (designated hereafter as Thomas Domes) are utilized for similarly exposing animals to atmospheric compositions of 100% oxygen or varying mixtures of oxygen and nitrogen at pressures ranging from ambient to as low as 5 psia (1/3 atmosphere). More detailed discussion on the design and operation of the THRU facility is published in references 5, 7, 8, and 14.

This report summarizes research accomplishments from September 1967 through May 1968. It includes a discussion of facility modifications and special equipment needed to meet changing experimental requirements and, more specifically, the rigorous fire safety requirements established by the Aerospace Medical Division. During the first three months of the reporting period, animal experimentation was conducted at a reduced level while maximum effort was expended to complete fire safety modifications, develop new standard and emergency operation procedures, and conduct training programs on the revised procedures for the research staff. The first Thomas Dome was reactivated on 21 December 1967. Experimentation in the remainder of the facility was phased-in over a six-week period, after which the THRU was back at the operational level which preceded the emergency curtailment of experiments in oxygen enriched environments following the tragic fires of Apollo I and the research chamber at the USAF School of Aerospace Medicine. This report also describes various facility experimental and operational problems and the status of experiments in progress as of 1 June 1968.

SECTION II

FACILITIES

GENERAL

Many of the various activities of the THRU, while important to the successful pursuit of the primary mission of the unit, are not of sufficient magnitude to merit separate technical reports. These activities will be reviewed under the general heading of "Facilities" and include the development or adaptation of computer programs, special projects in analytical chemistry, personnel training programs and special engineering modifications to the research facilities. A previous annual report (reference 5) presented preliminary discussions and proposed schematic diagrams of a number of equipment modifications that were completed during the current report period, therefore, the schematic drawings included in this report cover only those alterations made in the interim period.

COMPUTER PROGRAM SERVICES

Computerized data reduction and analysis programs have been used with increasing frequency during the past year. The BMD computer program library developed by the School of Medicine at UCLA has been drawn upon extensively. This excellent service of biomedical computer programs requires minor modification to fit the data output of the THRU. These modifications are accomplished mainly by the development of subroutine programs for variations in data size or type.

The BMD programs are classified into six categories reflecting six topical statistical concepts. The suffix of the program number corresponds to one of these categories. The categories are labeled as follows:

- (i) Class D - "General Description and Tabulation," 11 programs
- (ii) Class M - "Multivariate Analysis," 7 programs
- (iii) Class R - "Regression Analysis," 6 programs
- (iv) Class S - "Special Programs," 10 programs
- (v) Class T - "Time Series Analysis," 2 programs
- (vi) Class V - "Analysis of the Variance," 8 programs

Several of the forty-four programs such as certain members of Class V have been found useful although many will not be amenable to the biological data developed in our research operations. The programs which have already been used or which have been adopted for our use are described by their BMD classification numbers. These programs are compatible with the computer equipment available.

Class D, (BMD01D): "Simple Data Description"

Of the 11 programs in this class, BMD01D only has been used. This program tabulates the arithmetic mean, standard deviation, and standard error of the mean for an enormous number of variables (1000) allowing up to 99,999 cases for each. There exists the provision to select 17 transgenerations of the input data. In addition, the program will scan each variable and select the maximum and minimum value. For the remaining programs in Class D, several features are added to the capability of BMD01D especially the sorting, counting and general classification of a given variable into subsets. Some of these programs compile frequency tables (histograms) and sketch graphs. The computation of a correlation coefficient is a feature of several. In all, several of the programs in Class D will probably be used in the near future.

Class M, (BMD02M): "Regression on Principal Components"

This program computes the principal components of standardized data and ranks, descendingly, each standardized case by the relative size of the principal components. The method of principal components is one wherein linear functions over the random variables are constructed with each function having variance properties. The functions associated with the larger variance components constitute the functions of interest. The variables involved in these functions lead usually to the variables of importance, i.e., those worth studying extensively. Such an approach offers one a good exploratory tool; because a study might involve many independent variables which, if studied in one sequence, would be confusing and/or computationally prohibitive. The variables associated with negligible variances are deleted from the study, and a regression analysis is conducted upon the remaining variables.

Class R, (BMD05R): "Polynomial Regression"

This program is often used when the relationship between two variables is nonlinear. An example would be moderate departures from linearity such as a curved line describable by a second-degree polynomial. However, whenever there is doubt as to the degree of polynomial needed to describe the relationship, the program allows successive approximations to the empirical curve ranging from a first degree (linear) polynomial up to a tenth degree polynomial.

Class S, (BMD03S): "Biological Assay; Probit Analysis"

This program determines LD₅₀ values and the reciprocal of the slope coefficient for quantal response data. In addition, the fit of the regression line relating probit to dosage is tested. The program allows ten transgenerational routines, although the logarithmic transformation is almost universally

used in such problems. Some additional information has been added to the program to obtain confidence limits for the LD_{50} value; however, when using any transgeneration routine, the transformation to the scale of the original variable must be performed manually.

Class V, (BMD01V): "Analysis of Variance for One-Way Design"

This is the simplest form of variance analysis in which a single factor is analyzed. The program permits an unbalanced design allowing a sizable number of replications for each cell. Ten transgeneration codes are allowed. The output includes only the cell mean and the analysis of the variance table.

Class V, (BMD04V): "Analysis of Covariance with Multiple Covariates"

This program has been used extensively both for the purpose of studying the covariance relationship and for the output that this program yields, i. e., sum of squares, sum of products, and cell means. This tally is neatly arranged in an output section which allows easy construction of other meaningful results. Also, one may easily partition a set of data into subsets and obtain this same basic information for each subset merely by addressing a single sample size card to reflect this aim. The data output includes an analysis of the covariance table.

Class V, (BMD06V): "General Linear Hypothesis with Contrasts"

This test allows one to structure any testable linear hypothesis desired. Basically, the program utilizes the regression analysis model which can be set equivalent to an analysis of the variance (ANOVA) model in the case where three conditions hold: (1) uncorrelated residuals, (2) constant variance, and (3) zero mean. The regression model can be expanded to include 59 covariates; hence, the model implies a "general linear model" capable of supporting any general testable linear hypothesis over the parameters of the model. A feature of this program is that the hypothesis sum of squares is determined sequentially from each comparison (contrast) involved in the hypothesis, i. e., the hypothesis sum of squares is developed in a stepwise fashion. Hence, any hypothesis of greater than one degree of freedom must be constructed manually by adding the sum of squares of the respective mutually orthogonal comparisons. In essence, this usually results in a quite small amount of additional manual calculation.

Class V, (BMD08V): "Analysis of the Variance"

This program allows investigation of balanced designs only; however, given this feature, the program allows any combination of the following features to be incorporated into the design: factorial arrangements, nested

arrangements, and replicated measures. The latter feature permits the study of Kth order interactions. This is a comprehensive program; but, balanced designs are rarely applicable in biological studies.

The programs cited above are available at present and, as such, will likely handle most of the problems occurring at this (THRU) facility. As mentioned before, the programs available in Class M could open a relatively new type of investigation to be added to the present mode of investigation, i. e., add exploratory methods to the more comprehensive methods in present usage. Each program allows an assortment of transgeneration routines plus various other refinements. In many cases, a given amount of information may be obtained in a variety of ways using one of several programs even though one method is more appropriate to the given situation.

ANALYTICAL CHEMISTRY PROGRAMS

The primary function of the Analytical Chemistry Department of the THRU is to perform the routine tasks of monitoring animal exposure chamber contaminant concentrations, thus assuring the uniformity and reliability of controlled experiments necessary for meaningful interpretation of the measured biological responses. Preceding the regular analysis of chamber environments is the more challenging task of developing or modifying methods for the analysis of the contaminant to be tested. The ultimate goal of method selection or development in the THRU is continuous automatic monitoring.

Many analytical projects, although equally important, do not directly relate to the toxicological research in progress. These projects have to do with such things as the identification of pyrolysis products of potential space cabin materials. If the toxicity of the pyrolysis products is uncertain or unknown, the effort may then relate directly to the planning of toxicology research. These projects are discussed in this report.

Dichlorodifluoromethane

Dichlorodifluoromethane (CCl_2F_2), a well-known refrigerant gas, was under consideration for use as a space cabin fire extinguishant material. Since other halogenated hydrocarbons, particularly trichlorethylene (reference 12), have been shown to break down in life support systems with formation of more toxic end products, it was necessary to determine the fate of dichlorodifluoromethane when passed through a lithium hydroxide bed in the presence of moisture. An experimental apparatus was designed to accomplish this study. The apparatus consisted of a stainless steel vacuum chamber, a pump, and a lithium hydroxide canister in a closed loop. The chamber operating conditions for the experiment were 50% relative humidity, 98% O_2 , 5 psia pressure, and 2% dichlorodifluoromethane. This mixture was continuously circulated through the closed loop system for 48 hours. Samples of the gas mixture were removed periodically for analysis by gas chromatography.

A method developed for the quantitative analysis of dichlorodifluoromethane was capable of detecting as little as 2.5 ppb of this material in air as a lower limit. The technique, utilizing molecular sieve gas chromatography and electron capture detection, made use of conditions specifically designed to detect compounds both more volatile and less volatile than the test compound. Thus, if degradation to give compounds such as carbonyl fluoride or polymerization to give long chain fluorinated hydrocarbons took place, they should have been detectable. If the sensitivity to the products were similar to that of dichlorodifluoromethane, detection of degradation or reaction of the material to the extent of 0.1 ppm should have been possible.

Analysis of the atmosphere after 48 hours of operation, equivalent to 3000 cycles through the lithium hydroxide, revealed no peaks except that of the test fluorocarbon. Additionally, a portion of the lithium hydroxide bed was removed, dissolved in water, neutralized and analyzed for fluoride ion by means of an Orion fluoride electrode. The amount of fluoride determined by this method did not exceed the blank for unused lithium hydroxide. Thus, since neither volatile nor nonvolatile reaction products of dichlorodifluoromethane were discovered after recirculating in a dry, and 50% RH, 100% oxygen atmosphere, dichlorodifluoromethane is apparently stable under the conditions of the experiment.

Nitrogen Tetrafluoride (Tetrafluorohydrazine)

Among a group of propellant oxidizer materials to be subjected to toxicological investigation was nitrogen tetrafluoride (N_2F_4) which was subsequently removed from consideration due to a low interest priority. Prior to this time, considerable effort had been expended to develop an analytical method to determine N_2F_4 independent of any possible breakdown products or manufacturing impurities of this highly reactive compound.

Gas chromatography was studied as a possible means of monitoring N_2F_4 concentrations in inhalation toxicology experiments. The analysis of N_2F_4 is complicated not only by requiring a method capable of determining the presence of impurities but also by the formation of breakdown products of the N_2F_4 . There was evidence (reference 4) that N_2F_4 decomposed through an intermediate NOF, to NO_2 and HF in moist air. The complexity and corrosive properties of this material could not be handled by a nondispersive infrared analyzer or any other available continuous monitoring technique.

The first attempts to use gas chromatography in the analysis of propellant grade N_2F_4 were inconclusive. No chromatographic peak that could be identified as N_2F_4 eluted from a silica gel column which had been previously used in the assay of this material. Whether this was due to large amounts of impurities, complete adsorption by the column, or decomposition was not clear. The approach taken was to use a column packed with the most

inert column packing available. The column packing material selected was 40-60 mesh beads of Chromosorb T* coated with FC-43*. FC-43 is a fluorinated amine which possesses better coating properties than Kel F* oil and which might provide better separation of the N_2F_4 mixture. In order to minimize the effect of impurities, research grade N_2F_4 was used in all subsequent methodological investigations.

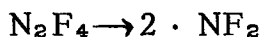
Since water vapor is known to catalyze the conversion of N_2F_4 to NO_2 , a drying system was incorporated into the dynamic oxidizer dilution manifold. The diluent gas passed through an apparatus consisting of a preliminary drying cartridge containing molecular sieve and a copper coil immersed in a dry ice bath. This reduced the water vapor concentration to about 1 ppm or 0.003% RH. The system was regenerated by heating the cartridge with nichrome resistance wire while purging with dry gas.

The N_2F_4 was transported to the chromatograph through 1/4-inch stainless steel lines which were part of a nitrogen- N_2F_4 dilution facility and through a 1.0 cc sample loop at the chromatograph. Before sampling of N_2F_4 was begun, these lines were purged with nitrogen. As the nitrogen eluted from the system, it was checked by infrared spectrometry. This technique disclosed that the lines had been heavily contaminated with nitrogen tetroxide from previous test runs. After all contamination had been removed from the lines by the nitrogen flushing, several gas chromatograms of nitrogen were recorded. The peak height was adjusted to a maximum on-scale reading by attenuating the power to the detector, after which no further instrumental adjustments were made. Several nitrogen peaks were recorded, to serve as reference standards, then N_2F_4 was introduced into the carrier gas flow stream. The height of the nitrogen peaks thereafter was closely observed. In addition to the peak for nitrogen, another peak appeared. The sum of the areas under the two peaks indicated that essentially all of the sample was eluting and, from the size of the second peak, that it probably was due to N_2F_4 . Several samplings were recorded for different concentrations of N_2F_4 in N_2 and a graph of the N_2 versus N_2F_4 peak areas was prepared. From the graph, we were able to estimate that no more than 7% of the sample was tied up in the column packing material and did not elute from the chromatograph. It also appeared that the chromatographic detector sensitivity was somewhat greater for N_2F_4 than for N_2 , but with only two peaks eluting, any impurities were being masked. Efforts were made to improve the resolution characteristics of this column by longer conditioning periods and by cooling the column considerably below the ambient temperature first used. The column initially showed good separative efficiency which, however, slowly deteriorated with continued use. Apparently the FC-43 was sufficiently volatile to bleed off slowly from the packing material, which meant that to use this technique for N_2F_4 monitoring would require frequent calibration and replacement of columns.

*Trade Name

Many different column lengths, packing materials and coatings were investigated. We finally determined that best separation with the least loss by absorption of N_2F_4 was achieved by using a 5-foot-long column packed with uncoated Porasil A* and subsequent work was conducted with this column.

Attempts were made to improve the analytical sensitivity of the gas chromatograph for N_2F_4 . Normally, doubling the power input to a thermal conductivity hot wire detector will increase the sensitivity eight fold. We had, however, switched from a standard tungsten detector to a special corrosion resistant nickel detector with an operating range of 250 to 350 milliamperes recommended by the manufacturer. While exploring the effect of various detector power levels on sensitivity, we determined that current levels above 200 milliamperes caused a decrease in sensitivity, and at 250 milliamperes we observed an inversion of the N_2F_4 chromatographic peak which could not be interpreted quantitatively. The observed negative peak indicated that N_2F_4 was producing a cooling effect on the sample side of the detector. This effect may have resulted from thermally induced dissociation of N_2F_4 into free radicals such as:



The detector power range found suitable for measurement of N_2F_4 was 70 to 150 milliamperes.

The chromatogram shown in figure 1 was produced while using the selected column and detector conditions described for the gas chromatography of propellant grade N_2F_4 . The N_2F_4 was diluted with nitrogen rather than air to prevent degradation. Four peaks were eluted from the column under these test conditions. These peaks were subsequently introduced into the mass spectrometer for further identification. Peak #1 is the N_2 used in the test gas mixture. Peak #2 contains NF_3 and CF_4 , and peak #3 contains C_2F_6 . The remaining peak, #4 contains both N_2F_4 and SF_6 . While using a column packed with molecular sieve 5A, we identified another impurity, C_3F_8 , of the propellant grade N_2F_4 . Occasionally, a peak identified as nitric oxide, (NO) was eluted from the column. Its erratic occurrence may have been due to oxidation to N_2O_4 during sample introduction.

Mass spectrometry and infrared spectrophotometry were utilized concurrently in the analytical research on N_2F_4 degradation in air. Table I lists the mass spectra of research grade and propellant grade N_2F_4 introduced into the batch inlet system and expanded into the mass spectrometer. The impurities in the research grade material are insignificant when compared with the propellant grade N_2F_4 . Present in significant concentrations in the propellant grade oxidizer are peaks due to NO, N_2O , HF, NF_3 , SF_6 and C_2F_6 .

*Trade Name

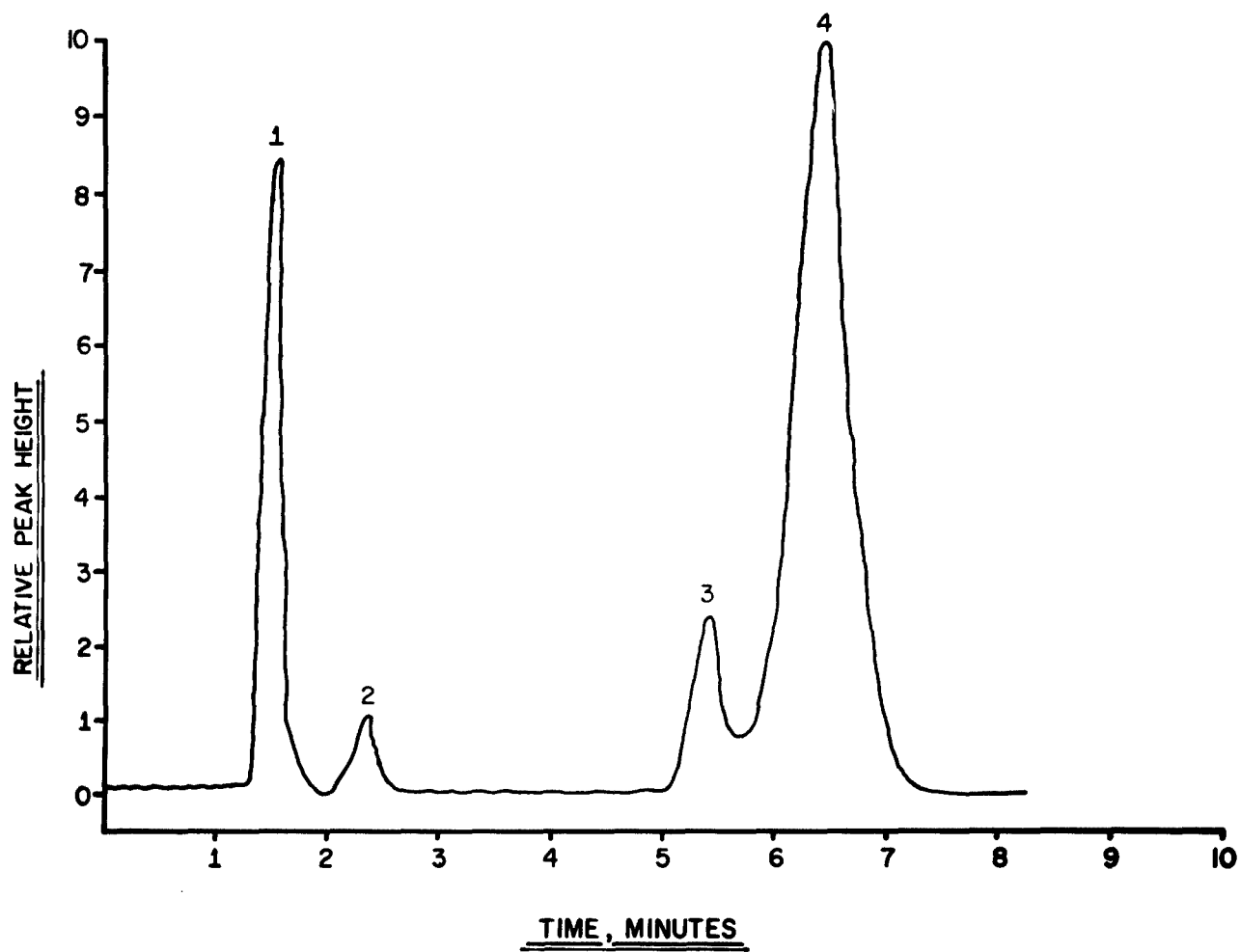


Figure 1. Gas Chromatogram of Propellant Grade N_2F_4

Table I

Mass Spectra of N_2F_4 , Unreacted and Chromatographed

	Mass Number	Assignment	Research Grade N_2F_4 Relative Abundance	Propellant Grade N_2F_4 Relative Abundance	Propellant Grade Chromatographed N_2F_4 Relative Abundance
1	14	N^+	8.04	6.5	
2	16	O^+	1.65		
3	18	H_2O^+	3.19	21.1	5.4
4	19	F^+	1.13	1.4	1.7
5	20	HF^+	1.75	13.2	6.1
6	27		1.85		
7	28	N_2^+	73.1	69.7	40.5
8	29		1.54		
9	30	NO^+	1.23	49.3	
10	32	O_2^+	24.4	16.9	
11	33	NF^+	100.0	67.4	81.2
12	34		2.27		
13	40		2.27		
14	44	N_2O^+	1.85	10.7	
15	47	N_2F^+	3.19	21.7	13.6
16	52	NF_2^+	78.1	100.0	100.0
17	53		1.96		
18	64	CF_2N^+		2.5	
19	66	N_2F_2^+	1.65	28.2	4.7
20	69	CF_3^+		63.0	5.3
21	71	NF_3^+		3.7	
22	85	N_2F_3^+	1.75	34.1	4.5
23	104	N_2F_4^+		21.4	
24	119	CF_3CF_2^+		20.3	
25	127	SF_6^+		10	

Included in table I for comparison is the spectrum of propellant grade N_2F_4 , which had been chromatographed directly into the mass spectrometer and which is similar to the spectrum of research grade N_2F_4 .

Infrared spectrophotometry of the oxidizers largely confirmed the conclusions drawn from gas chromatography and mass spectrometry concerning the impurities in propellant grade N_2F_4 . Figure 2(b) is an IR spectrum of the research grade oxidizer and matches the spectrum of pure N_2F_4 as seen in the literature. Figure 2(a), obtained from the propellant grade material, shows peaks which can be assigned as in table II.

Table II

Infrared Identification of Propellant Grade N_2F_4 Impurities

<u>Peak</u>	<u>Wavelength Microns</u>	<u>Assignment</u>
A	7.7	CF_4
B	8.1	C_2F_6
C	9.1	C_2F_6
D	10.5	SF_6
E	11.1	NF_3

No infrared evidence of NO, N_2O , or C_3F_8 was obtained, but NO and N_2O have poor infrared sensitivity and require relatively large concentrations for detection by this technique. C_3F_8 , if present, would have an absorption spectrum quite similar to C_2F_6 and might, therefore, be hidden.

An infrared study of the degradation of N_2F_4 in air was undertaken and is illustrated in figure 3. The sequence of spectra confirm the course of reaction elucidated by Dost et al (reference 4). Figure 3(a) is the pure N_2F_4 spectrum before addition of air. Figure 3(b) is the spectrum 8 minutes after the addition of air and is essentially a spectrum of NOF with a small amount of N_2O_4 . In figure 3(c), 24 minutes after air addition, the concentration of NOF has decreased and that of N_2O_4 increased. In addition, new peaks at 3.5 microns and 5.8 and 5.9 microns indicate the possible production of HF and NOCl (possibly from reaction of NOF with the cell windows). In the last spectrum, figure 3(d), 60 minutes after air addition, NOF has almost completely disappeared, the cell containing mostly N_2O_4 and possibly HF and NOCl.

The same series of reactions apparently occurred with propellant grade N_2F_4 but at a much faster rate than with the research grade. For example, it took 60 minutes for complete conversion of research grade N_2F_4 to N_2O_4 ; whereas the same conversion took place in about five minutes with propellant grade, although the degradation time was quite variable and seemed to be subject to many influences. The presence of NO in the propellant grade N_2F_4 may account for the increase in reaction rate with air, since it is known that the following reaction takes place readily in air:

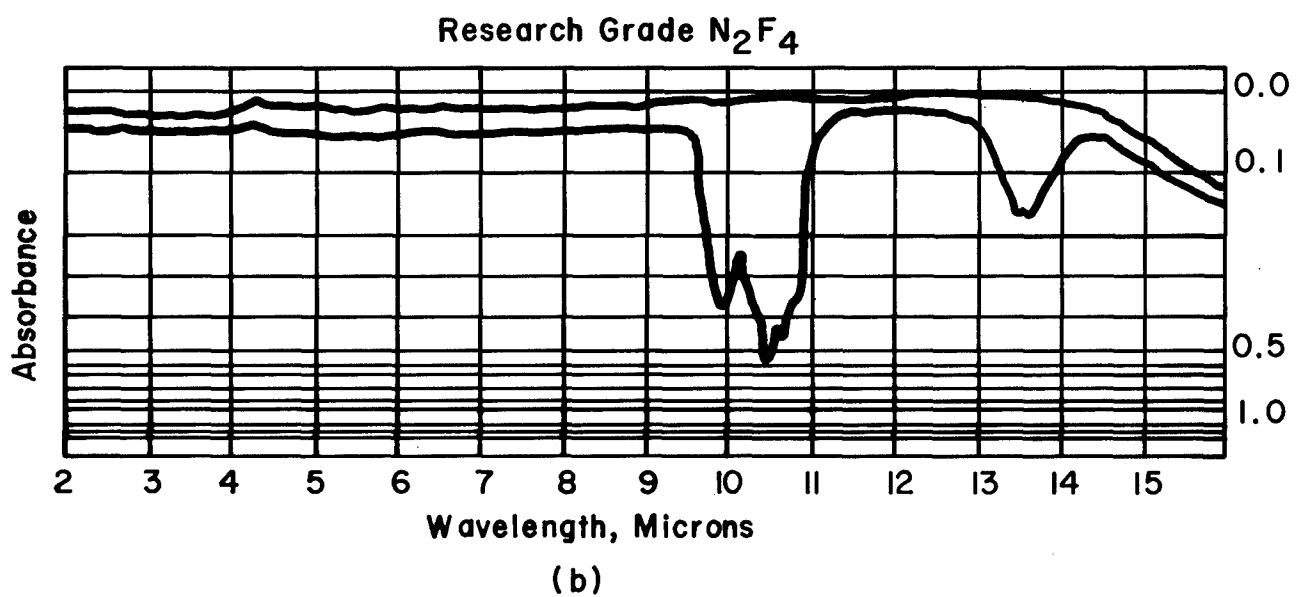
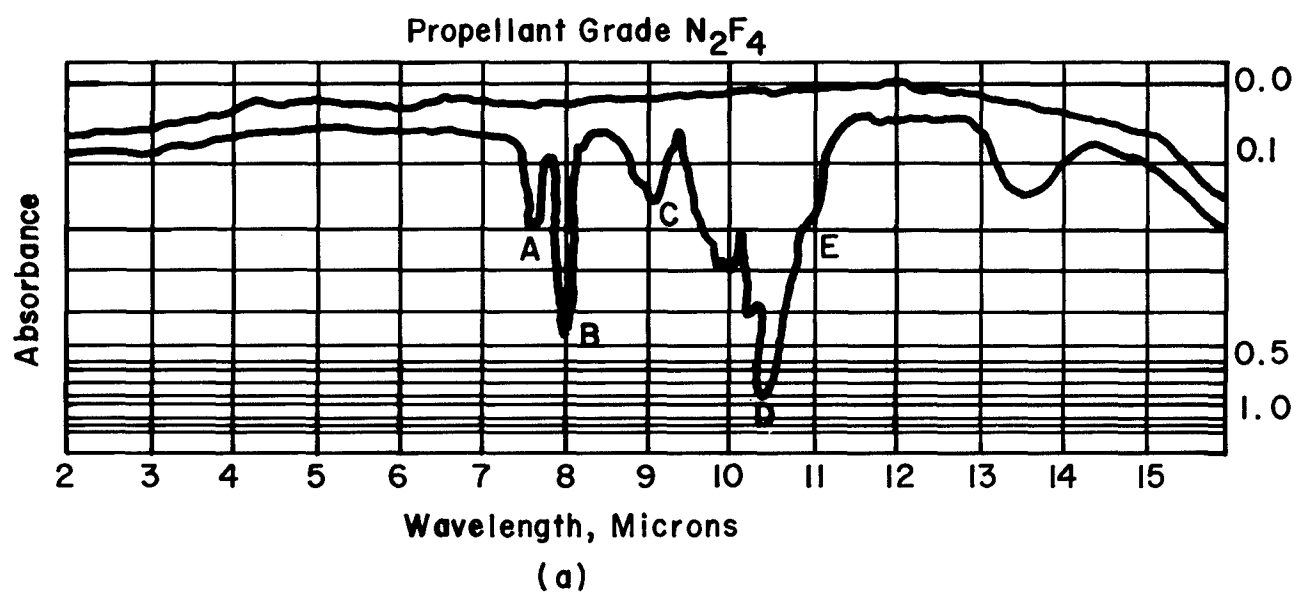


Figure 2. IR Spectra of Unreacted Research and Propellant Grade N_2F_4

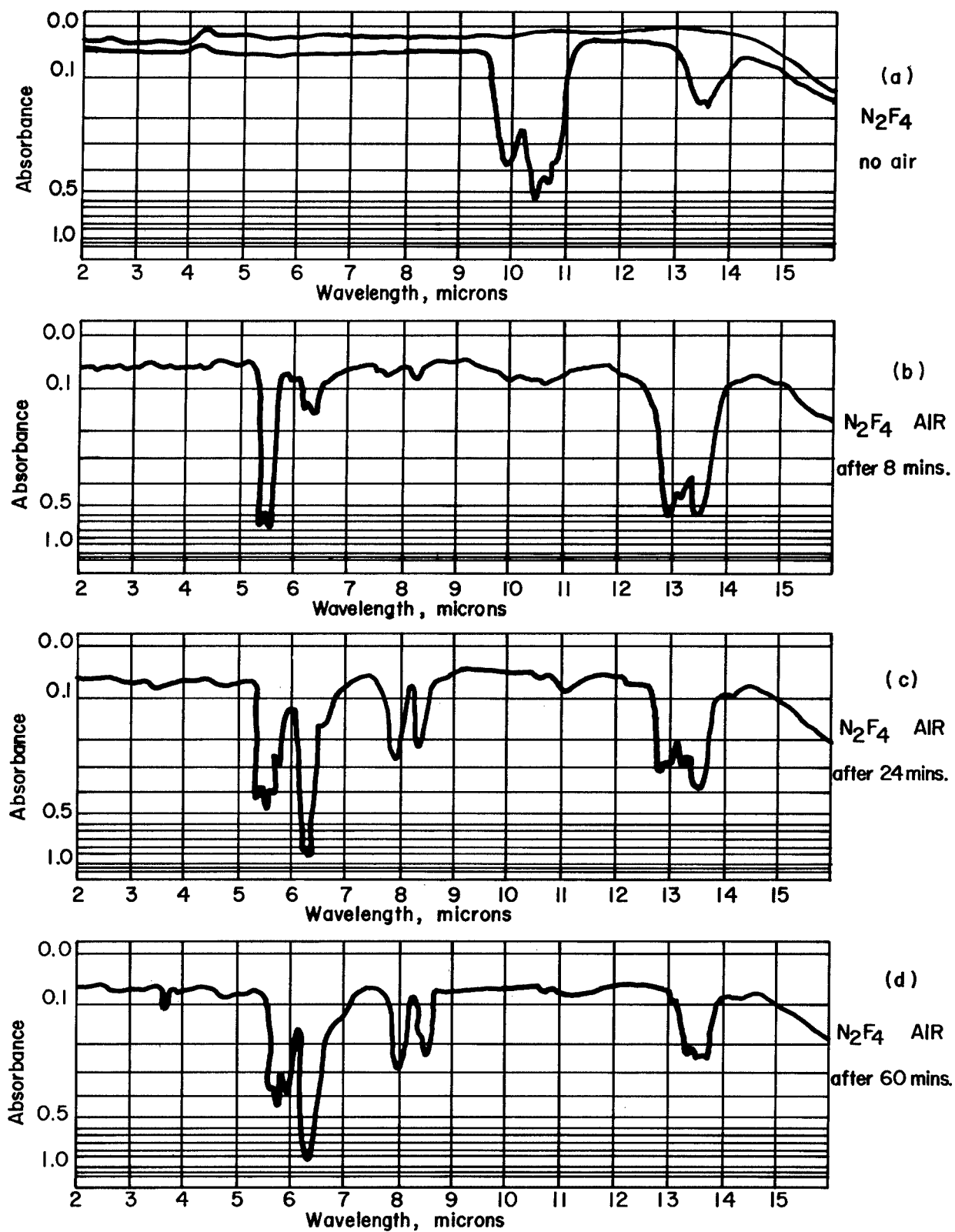
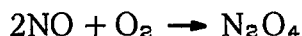
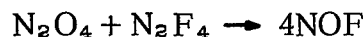


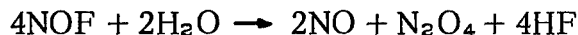
Figure 3. Decomposition of Research Grade N_2F_4 in Room Air



Then



And, as proposed by Dost et al (reference 4):



Thus, NO would be catalytic for the degradation of N_2F_4 in air.

The combined use of infrared spectrophotometry, mass spectrometry and gas chromatography led to the successful characterization of the impurities present in propellant grade N_2F_4 . The course of N_2F_4 degradation in air elucidated by Dost was confirmed as:



This degradation occurred at a much faster rate with propellant grade N_2F_4 than with research grade, possibly due to the presence of NO in the former material. Efforts to develop a method for quantitative measurement of low N_2F_4 concentrations were stopped when this material was reassigned a low interest priority.

Carbon Monoxide

Carbon monoxide concentrations in the Thomas Dome were monitored using a nondispersive infrared analyzer with a measuring cell path length of one meter. Although this instrument was equipped with a filter cell for the elimination of minor interference by carbon dioxide and water vapor, the high and variable levels of these vapors in the dome atmosphere necessitated that they be removed before introduction into the IR cell. Therefore, a chiller system for condensation of water vapor and a canister of lithium hydroxide for carbon dioxide removal were installed in the sampling line. With these additions to the system, the improved analytical precision permitted close control of the carbon monoxide chamber concentration at both ambient and reduced pressures.

The chamber contaminant introduction system for carbon monoxide included a reaction chamber for the degradation of iron pentacarbonyl when individual supply cylinders of CO contained significant concentrations of this contaminant. The possibility of contamination in steel cylinder stored CO was reported by Brief et al (reference 2). The reaction chamber consisted of a 3/8-inch copper tube filled with copper shavings around which nichrome heating wire had been wrapped. The tube was heated to 400 C at which temperature iron carbonyl decomposes to the metal and carbon monoxide. An analytical method reported by Brief was adapted to monitor the concentration of CO in

cylinders used for animal exposures. The cylinders were monitored at weekly intervals until all available CO was consumed. The results of the weekly monitoring showed that some increase of iron pentacarbonyl formation occurred with decreasing pressure. At no time, however, did the concentration of iron pentacarbonyl in the cylinder exceed 10 ppm, a value which represents a maximum exposure concentration of 0.0005 ppm and is well below physiologically toxic levels.

ENGINEERING PROGRAMS

Growing emphasis has been placed on the continued development and improvement of preventive maintenance programs during the past year, and some important modifications were undertaken. Much of the scheduled routine preventive maintenance is performed by the shift engineering technician who also provides emergency maintenance. The success of this preventive maintenance was noteworthy in attaining maximum dome utilization except for that period during which the required fire safety modifications were being installed.

Fire Safety Modifications

A comprehensive review of the Thomas Domes was conducted by a committee appointed by the Aerospace Medical Division. This committee compiled a series of recommended modifications for improved fire safety. Compliance with these recommendations was necessary to obtain approval for the conduct of experimental operations in oxygen enriched atmospheres. Most of the recommended changes were relatively minor and were accomplished with minimum effort. The major requirement was for an automatic, quick-acting fire sensing system to activate a water deluge system. An automatic system which exceeded the AMD requirements was designed and subsequently installed in the Thomas Domes. The key component of the fire protection system is the UV sensor, shown in figure 4, five of which are mounted in the top of each dome and positioned to scan the entire surface of the dome floor. A sixth UV sensor is mounted in the airlock of each dome. The sensors were required to respond to the detection of flames within 0.2 seconds by activating the water deluge system. Under actual test conditions, the sensors have responded to the flame from a paper match located approximately 12 inches above the dome floor. A signal from the UV sensor to a timed relay activates a pair of solenoids in the pilot pressure line, as shown in figures 5 and 6, to the water ring within the dome. The first solenoid shuts off the water supply to the pilot pressure line and the second opens a drain valve. The resultant pressure drop opens a valve in the individual sprinkler heads and the dome fire is deluged with water. Twenty-four sprinkler heads are mounted in two circular rings, as shown in figure 7, in such a manner as to spray water in every direction so that a fire could not continue to burn in isolated areas.

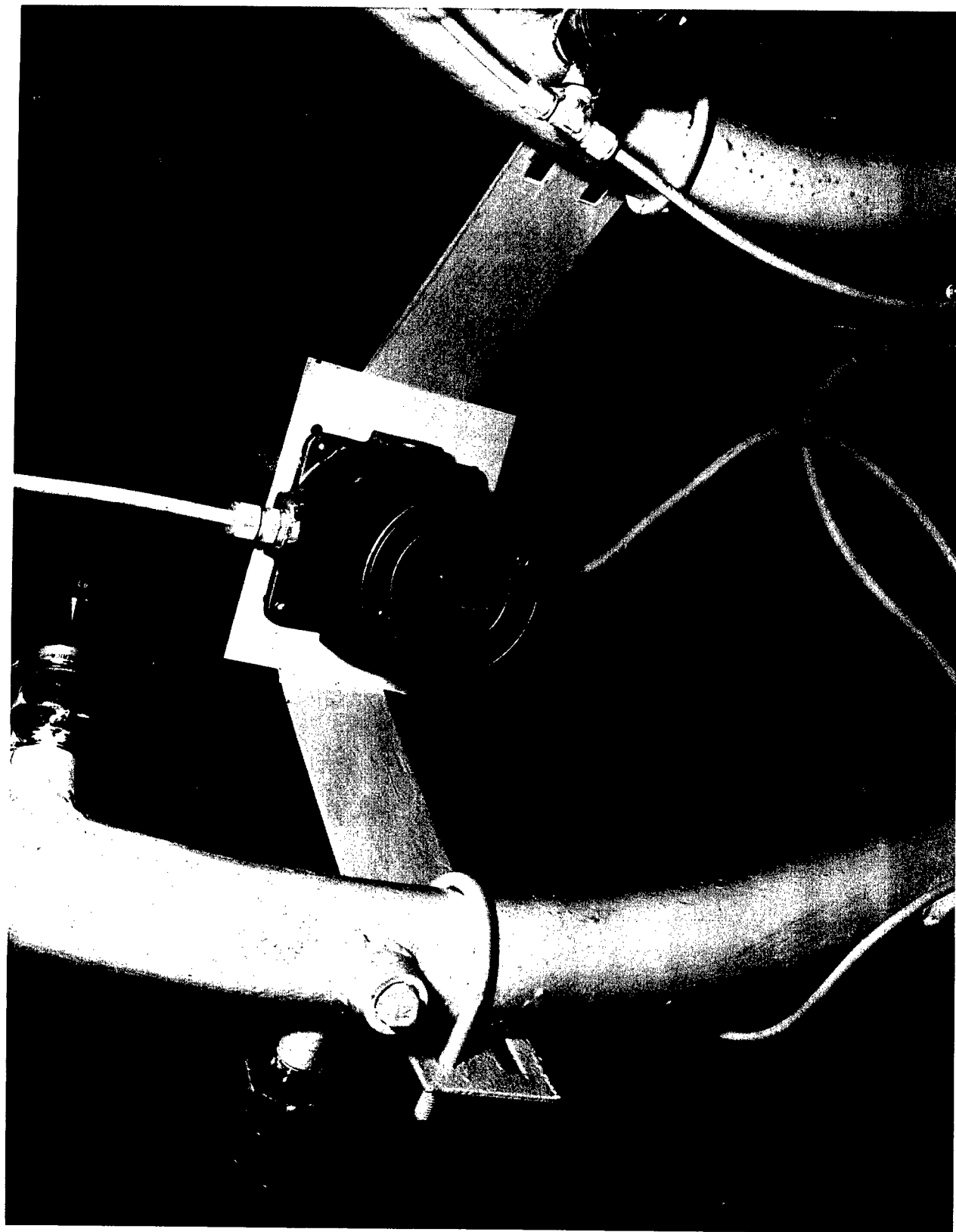


Figure 4. UV Sensor in Dome Mounting

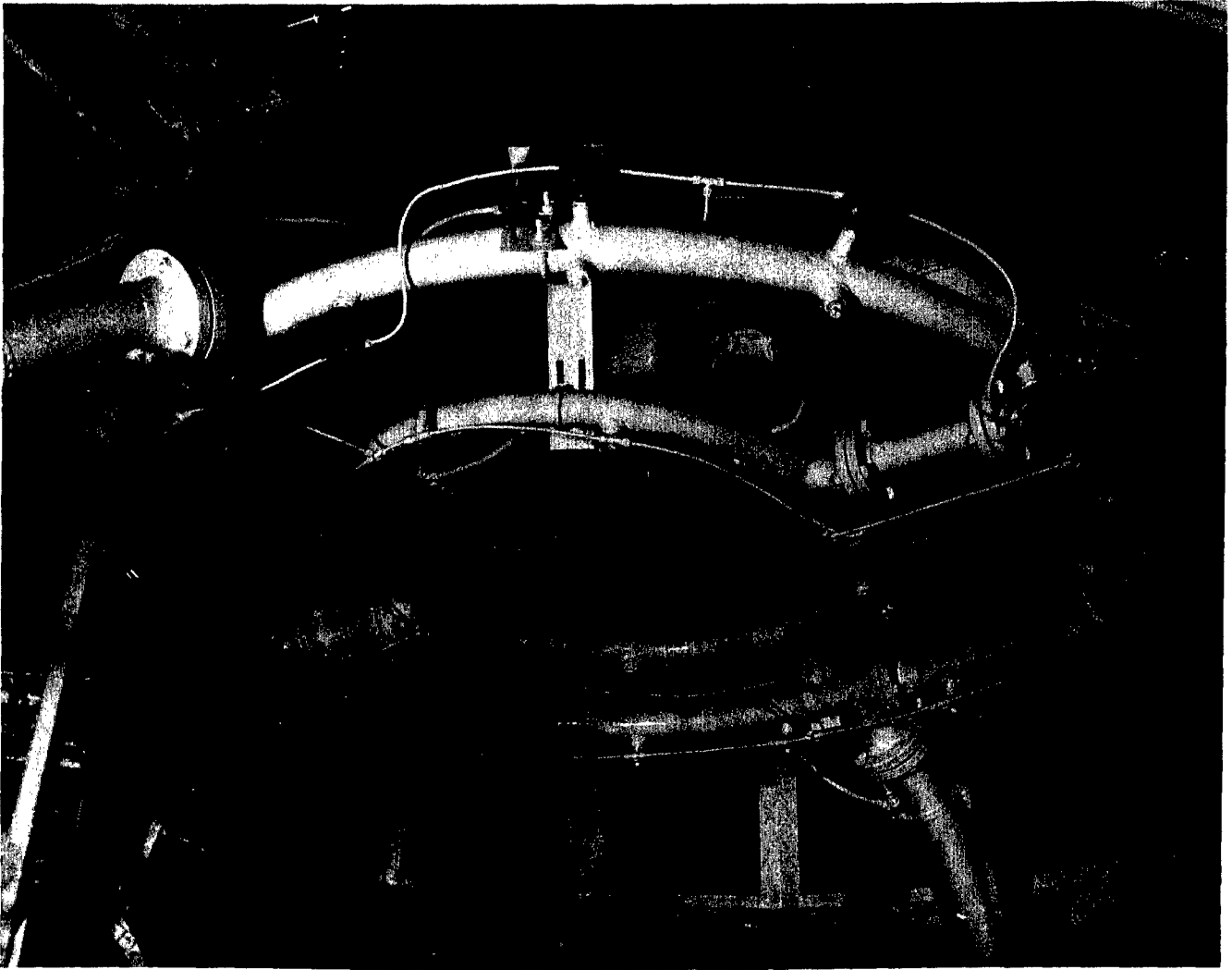


Figure 5. Dome Sprinkler System, Including Pilot Pressure Lines

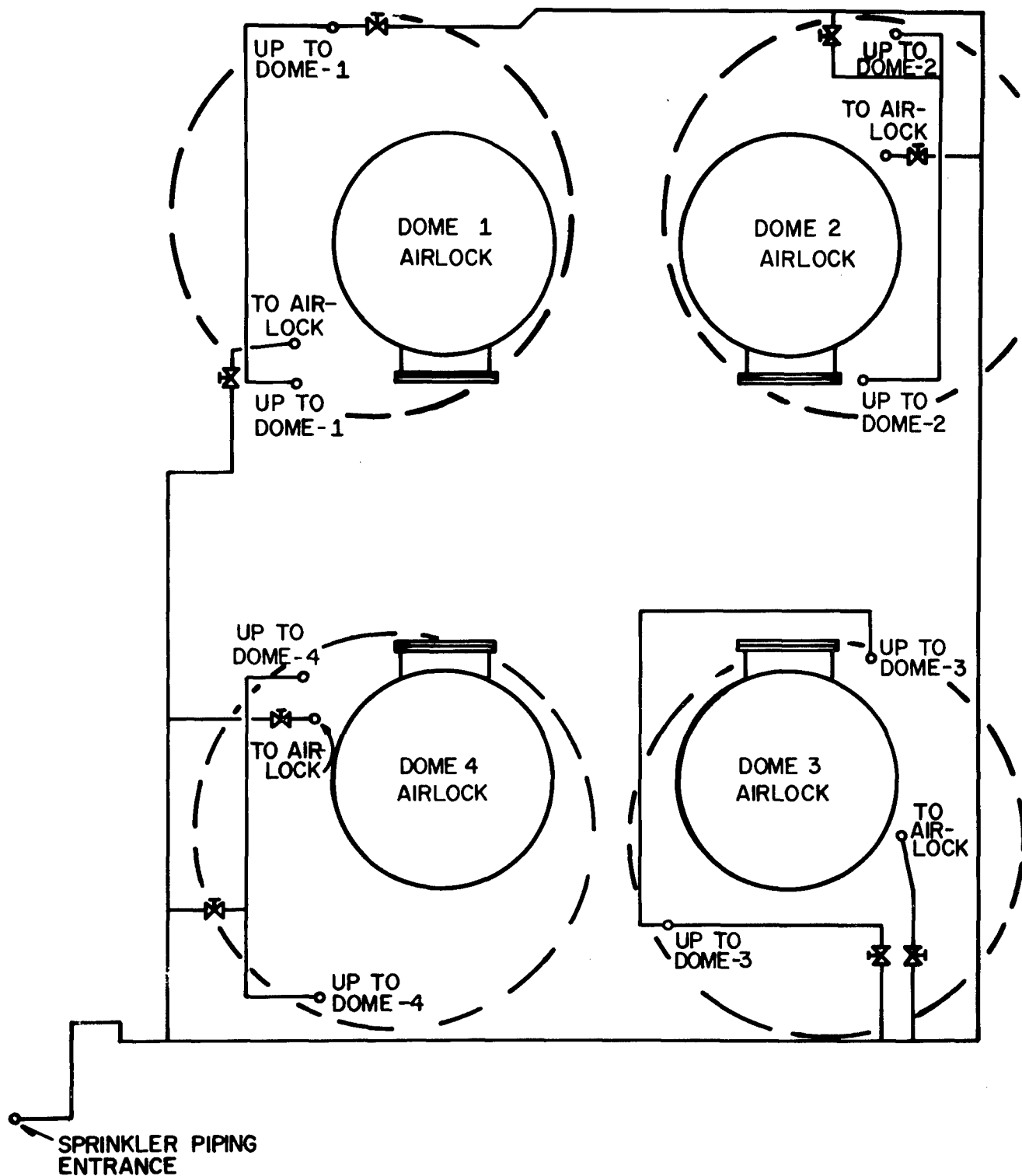
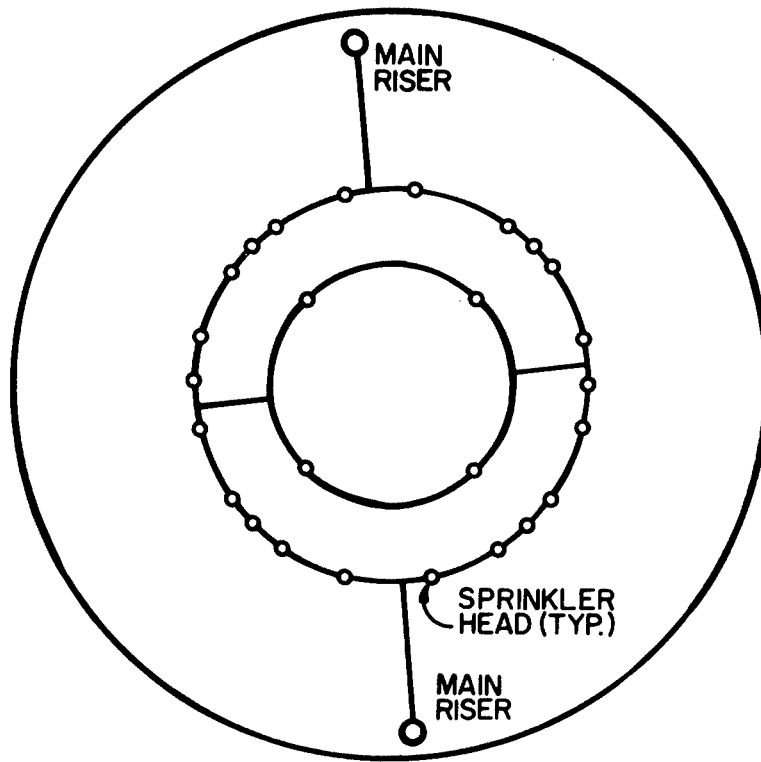
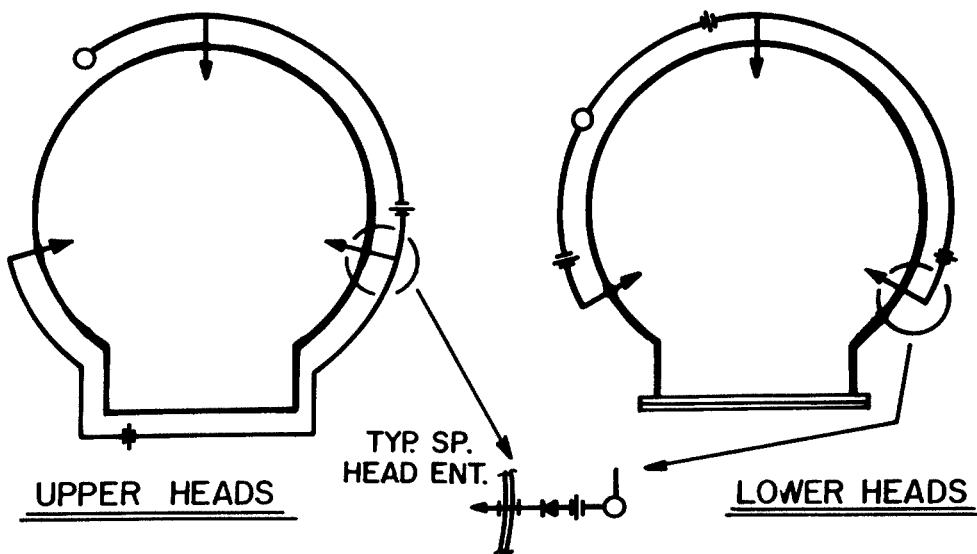


Figure 6. Dome Sprinkler System, Main Piping Diagram



TYPICAL DOME SPRINKLER HEAD LAYOUT



TYPICAL AIRLOCK SPRINKLER HEAD LAYOUT

Figure 7. Dome Sprinkler System, Sprinkler Head Layout

At the end of twenty seconds, during which water has been spraying the dome at the rate of 850 gallons per minute, the timed relay closes the pilot pressure line drain valve and reopens water pressure. This action immediately closes the valve in the sprinkler heads, stopping water flow in the domes. The relays in the system automatically reset within five seconds. The dome airlock sensor, which operates independently from the dome above, follows the same sequence of events.

Manual override valves have been installed both inside and outside of the domes and airlocks as added safety precautions. These override valves directly relieve the pressure in the pilot line to activate the sprinkler heads independently from the automatic controls and, therefore, must also be turned off manually to stop the water flow within the dome.

The fire protection system master control panel, shown in figure 8, is provided with key lock switches so that the system cannot accidentally become activated. The automatic mode of operation is always used when THRU personnel are inside the dome. To minimize the possibility of accidental activation when no dome entrant is present, the controls are locked in the manual mode. The master control panel also automatically performs several related emergency functions when a fire is sensed.

During a fire, the following actions are accomplished: (1) automatic isolation of dome gas flow and pressure valves, (2) cut-off of chamber power, excluding lighting, (3) activation of the fire department call box, (4) activation of the building evacuation alarm, and (5) optional repressurization of the dome.

The control modes, both automatic and manual, (see block diagrams in figure 9), now available for the operation of the Thomas Domes sprinkler system are as follows:

A. Fire System Detection - Automatic Mode (Fire in Domes - Dome Entrant)

Activates:

1. Dome Sprinkler System
2. Fire Department Call System
3. Building Evacuation Alarm
4. Isolation of Domes
5. Cut Off Dome Power (Excluding Lighting)
6. Repressurization of the Fire Dome (Optional)

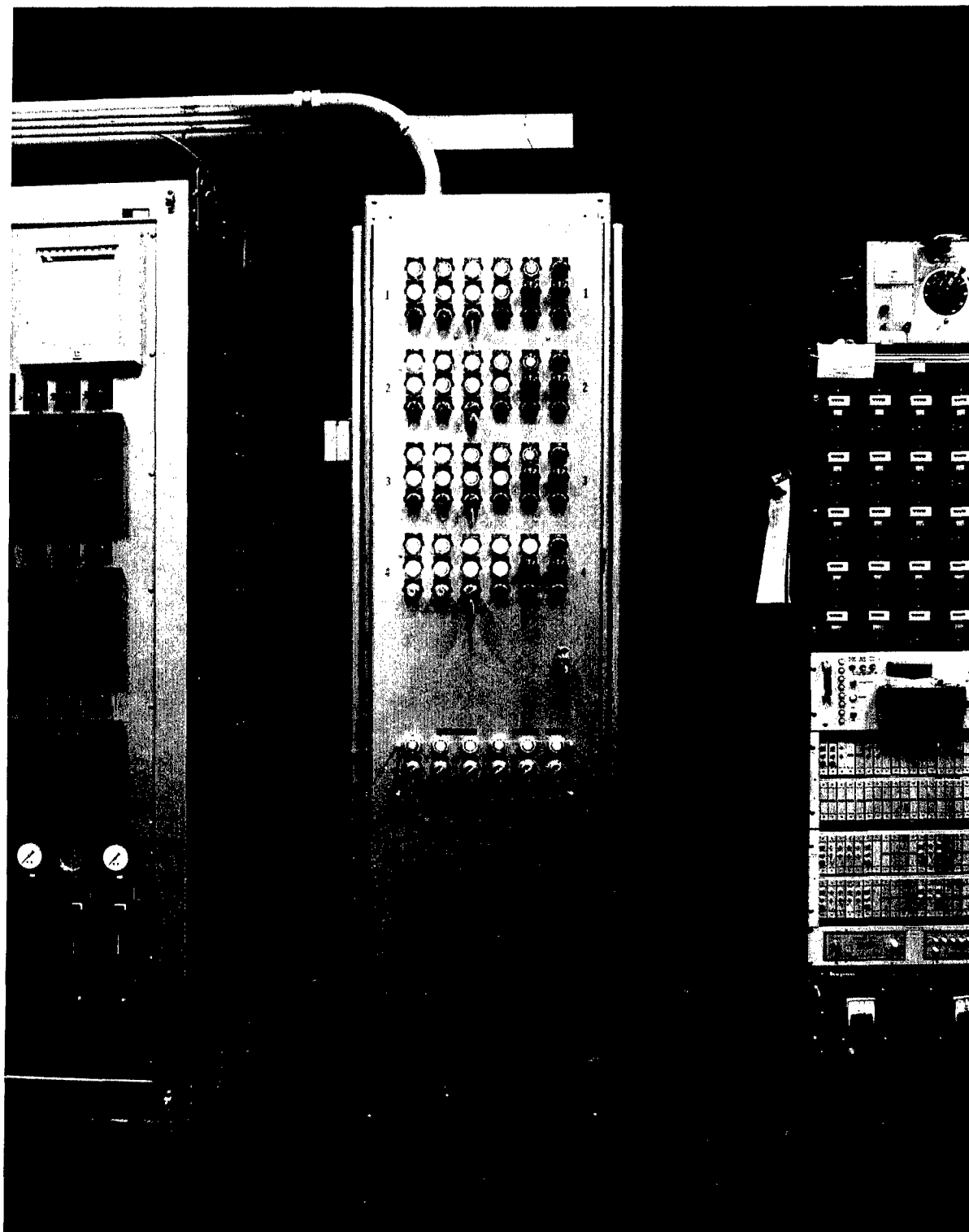


Figure 8. Dome Fire Protection System, Master Control Panel

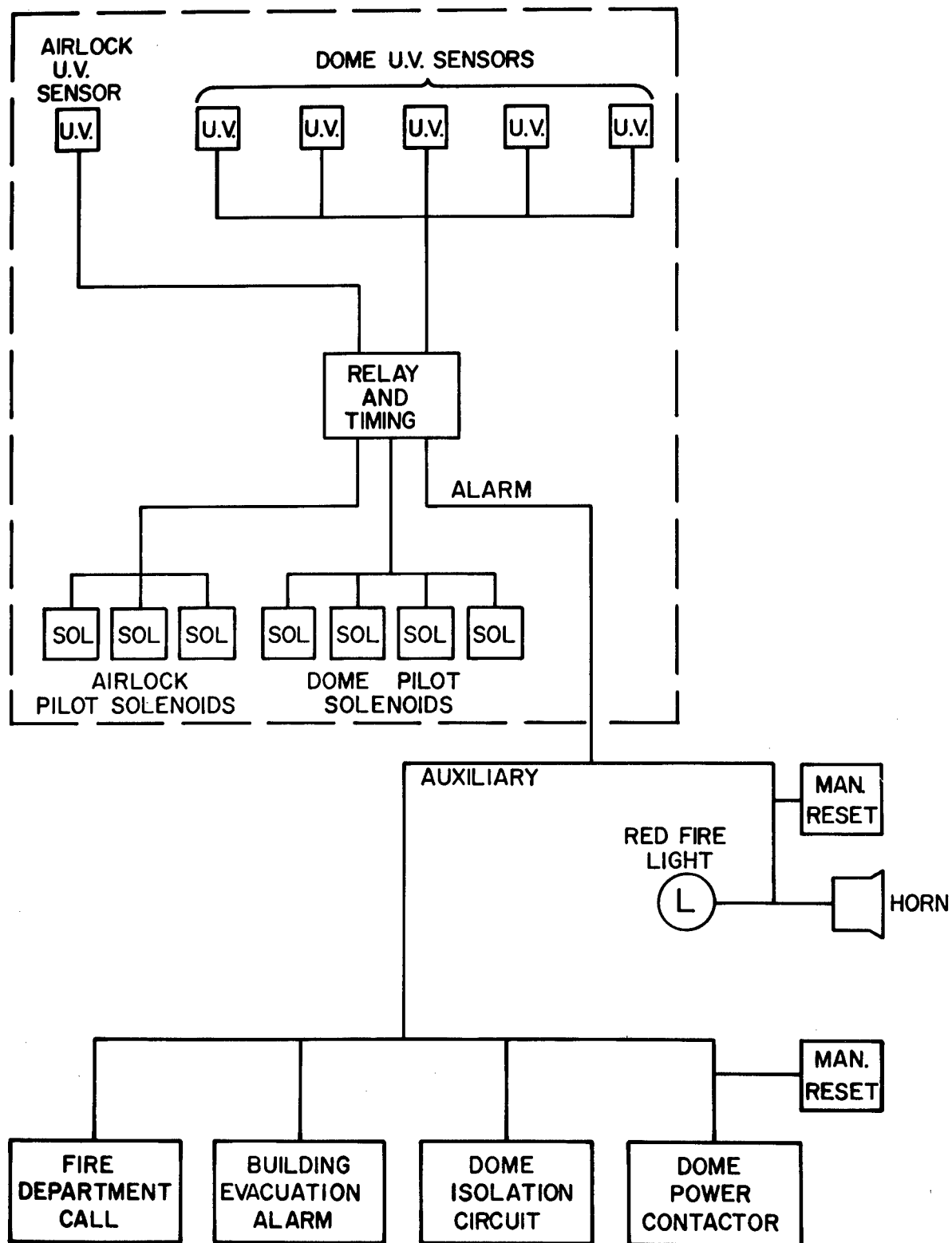


Figure 9. Dome Fire Protection System, Block Diagram

B. Fire System Detection - Manual Mode (Fire in Domes - No Dome Entrant)

Activates:

1. Fire Department Call System
2. Building Evacuation Alarm
3. Isolation of Domes
4. Cut Off Dome Power (Excluding Lighting)
5. Repressurization of the Fire Dome (Optional)

These modes of operation provide maximum protection for dome entry due to the speed of response of the fire system, yet provide automatic detection of fire conditions with manual activation of the water system when there are no entrants present in the chamber. Operation in the latter mode prevents the occurrence of accidental triggering of the water sprinkler system with concurrent loss of experimental data. The fire department call system is inoperative at the present time due to construction work in progress for four more Thomas Domes. When the construction work on the new building addition is completed and the fire alarm is reinstalled, the two systems will be tied together, and an outbreak of fire in a dome will automatically alert the fire department.

Handles are fastened to two places on one window in each dome, and all clamps are removed when pressure in the dome is reduced. The handles are painted red to call attention and to be readily visible. This modification was provided to permit dome entrants to leave the dome quickly in an emergency or to provide fast entry for personnel rescue action after repressurization of the dome.

A careful review of standard and emergency operating procedures, as also recommended by the AMD Safety Committee, resulted in extensive revisions to both sets of procedures. Major emphasis was placed on including a change due to equipment additions and modifications. The greatest emphasis was placed, however, on simplification of all procedures, many of which had become more complex during previous revisions.

The main alarm system for the Thomas Domes was modified to provide an Observer C call button. This modification was made to meet a requirement of the revised Standard Operating Procedures which specify that an Observer C either be present or readily available during any dome entry. Observer C must also be present when the dome entrant is passing either in or out of the airlock system. The call signal was provided by modifying the

main alarm system to sound a pulsing horn signal at the rate of 60 per minute. The switch for activating the signal is a maintained contact toggle switch located on the master control panel CP-A1. This switch is to be activated by Observer A to call Observer C and will remain activated until Observer C deactivates it.

Oxygen Distribution System

A series of modifications, shown in figure 10, were made in the gaseous oxygen supply distribution system to permit dome repairs and to simplify oxygen delivery to face-mask systems. The original O₂ supply system to the domes consisted of one continuous pipeline. In the event of malfunction or defective equipment in any one dome, it was necessary to shutdown all domes to effect repairs. Individual manual shutoff valves were installed in each dome line, enabling any one of the four systems to be isolated from the other three.

Concurrent with the installation of shutoff valves, the prebreathing and breathing oxygen systems for dome entrants were modified. The standard A-14 O₂ regulators in the domes, airlocks, and prebreathing room were connected to the dome O₂ supply line, thus eliminating the need for the breathing O₂ manifold located in the basement. This modification eliminated a number of problems associated with obtaining cylinder supplies of oxygen in large quantities and transporting them to and from the use area. As an emergency back-up system in event of failure of the main O₂ supply, equipment was designed and installed to provide automatic switchover to standby O₂ cylinders. The emergency cylinders contain 400 cubic feet of gas oxygen, a sufficient supply for the safe exit of personnel from the domes should such action become necessary.

The pass-thru locks installed in each dome are also being supplied with O₂ from the main O₂ supply system for purging purposes. Originally the locks were supplied from the breathing O₂ manifold system.

To permit safer elevation of the dome cap during an emergency, automatic disconnects have been installed in the two lines providing H₂O and O₂ to the dome top. Originally, the H₂O supply had a pressure type disconnect and for the O₂ supply, a thin-wall aluminum tube was used. Both of these items imparted a lateral motion to the dome cap when emergency lifting was attempted. The automatic disconnects installed are spring loaded, with the weight of the dome top providing sealing for the H₂O and O₂ supplies. Double shutoff type valves are used providing automatic closing of the supply lines when the dome cap is lifted.

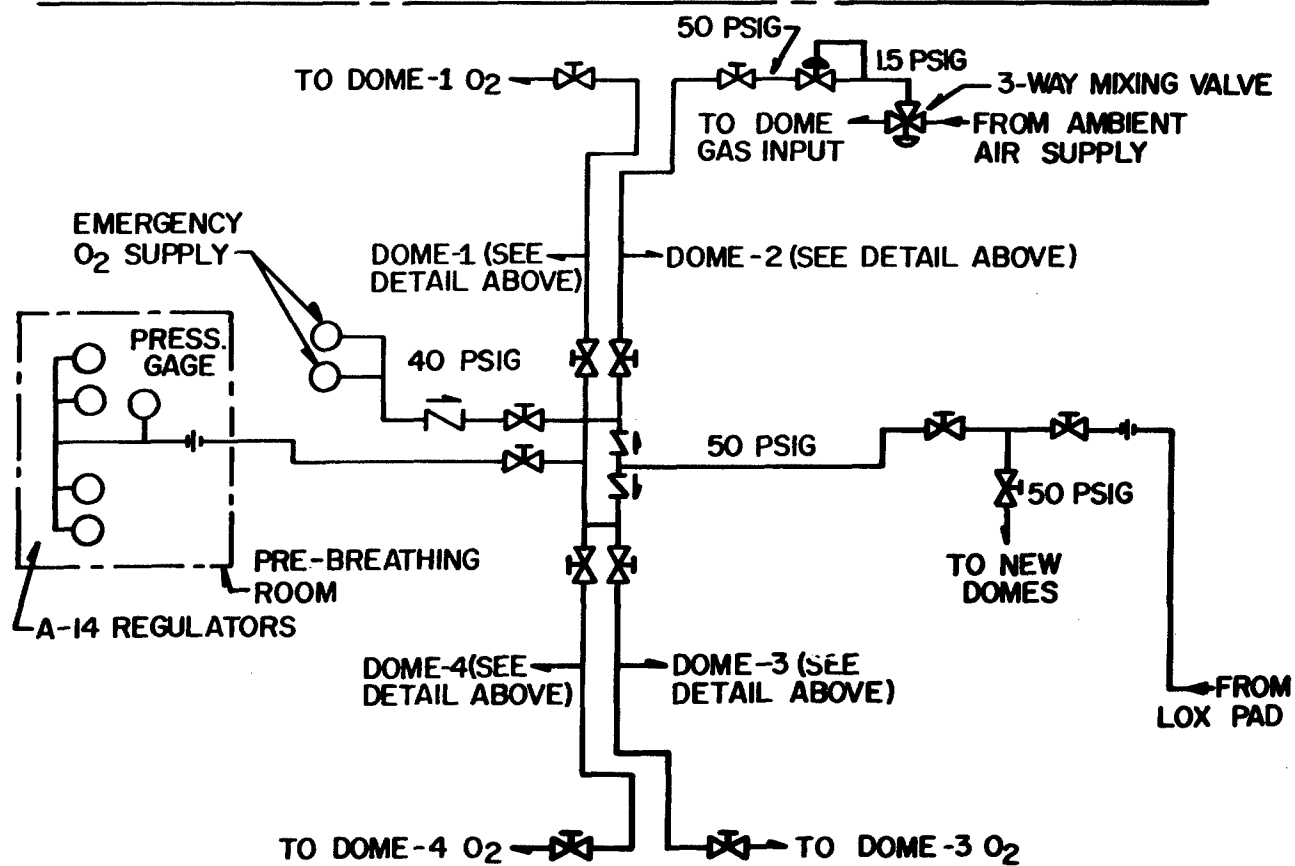
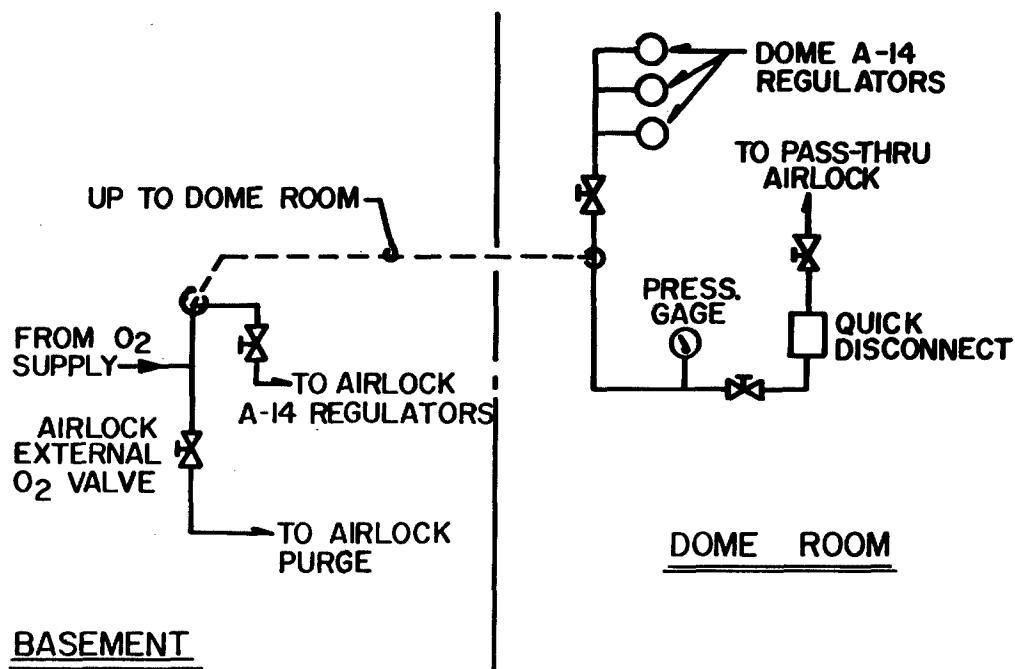


Figure 10. Dome O₂ Supply System

Two-Speed Crane

The overhead crane for lifting dome tops was originally designed for high speed lifting for emergency purposes. In actual operation the crane's high speed created problems in the routine raising and lowering of the dome top. Consequently, the unit was modified to permit two-speed operation, retaining the emergency hoist rate of 18 feet per minute and adding a normal operating rate of 4.5 feet per minute.

Automatic Control of Relative Humidity

The automatic humidity control system for the Thomas Domes atmosphere, which was designed shortly before cessation of oxygen-rich experimental environments early in 1967, was installed and checked out first in Dome 4. Due to the nature of control required in the O₂ atmosphere and 5 psia conditions, it had been impractical to calibrate and adjust the system until such environments could be used. After adjustment of equipment to the operating conditions, automatic control of the relative humidity has proven to be very satisfactory, with variations in relative humidity averaging less than plus or minus 5 percent. Since the system proved satisfactory and practical, it was subsequently installed in the other three Thomas Domes.

The wet-bulb/dry-bulb temperature measuring probes are stainless steel thermistor units. All auxiliary equipment was fabricated in the THRU shops. The supply and signal connection lines to the probes are enclosed in stainless steel tubing. Several methods were considered for providing water to the wet-bulb wick, and it was decided to utilize a manually-filled reservoir rather than an automatic type. This has reduced necessary preventive and corrective maintenance in the dome. The wet-bulb reservoir is manually filled from the exterior of the dome.

Calibration Gas Supply System

Calibration gases are required on a daily basis for use with four separate instrumentation control or monitoring panels as listed below:

1. CP-A4 - Dome Oxygen Monitoring and Control Panel
2. CP-A5 - MOL Monitoring and Control Panel
3. CP-A2 - Apollo Monitoring Panel
4. CP-A6 - Dome CO₂ Monitoring Panel

Each console unit requires a minimum of two gases for zero and span calibration adjustment. A common supply system (figure 11) was designed to serve each console, reducing the number of gas cylinders stored in the facility and, thereby, improving safety and housekeeping aspects in the dome area.

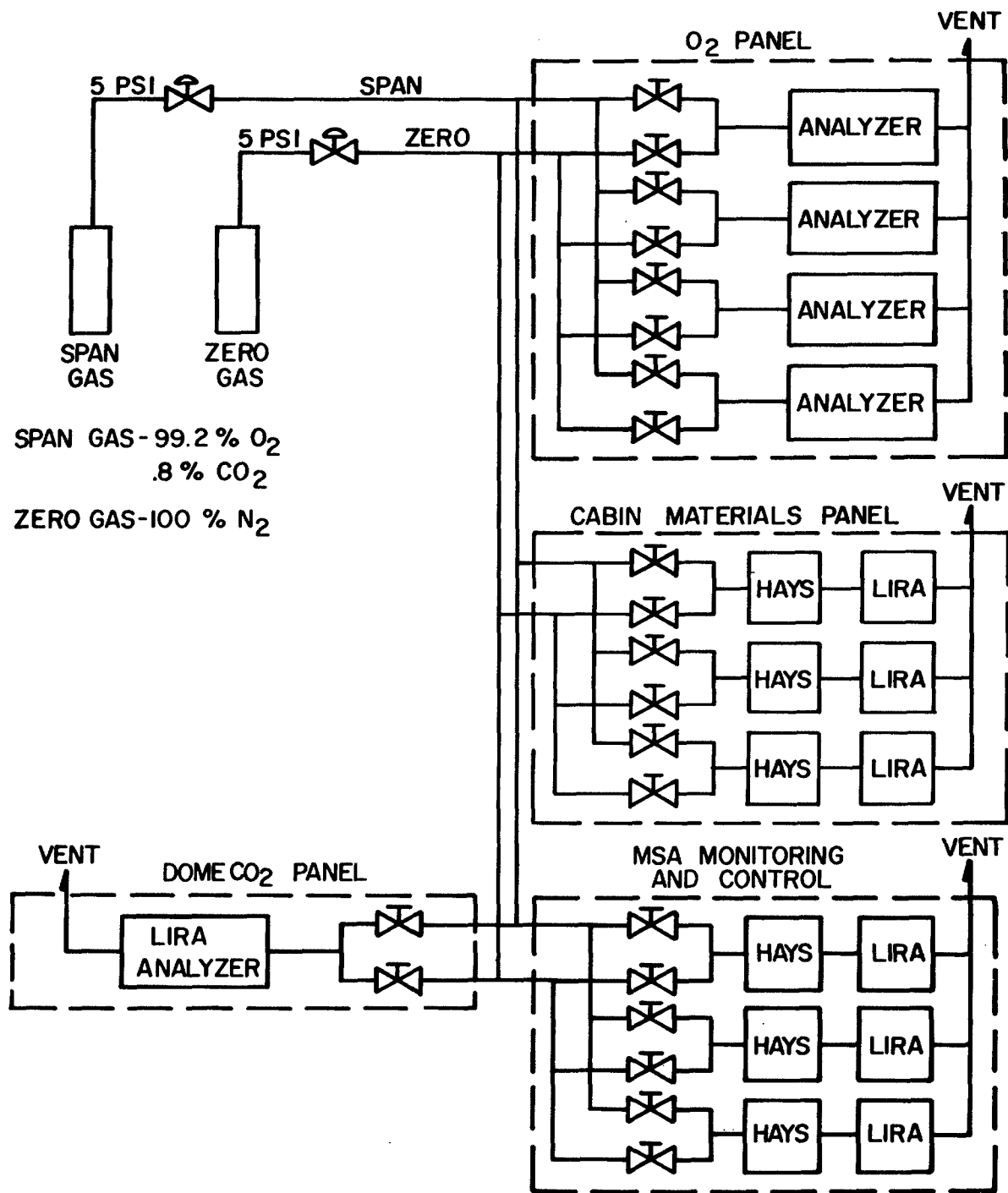


Figure 11. Calibration Gas System, Flow and Block Diagram

Nitrogen is used as the zero gas for environmental monitoring instruments while the span gas is composed of 0.8% CO₂ and 99.2% oxygen. The O₂ content of the span gas is used for calibration of paramagnetic oxygen partial pressure analyzers and the CO₂ for calibration of nondispersive infrared CO₂ analyzers.

Cabin Materials Toxicity Screening System

The design for a closed-loop life support system to be used for exposure of rodents to space cabin construction material gas-off products was described in the previous annual report (reference 5). The fabrication of the system and its installation in Dome 1 was completed during September of 1967, but it could not be completely tested until the required new fire sprinkler system was completed. This life support system was similar to the design used for Apollo space cabin materials testing, except that it allowed the use of mixed gas environments at reduced pressure. As oxygen was consumed for animal metabolism it was replaced by the opening of a two-way pressure relief valve to the dome outer envelope operating with a 100% O₂ atmosphere. Inert gas losses are made up, if needed, from cylinder gas storage. Before actual use of the new system began, a decision was made to install an atmosphere bypass around the lithium hydroxide CO₂ scrubber to allow animal exposures in a CO₂-enriched environment more similar to that surrounding an astronaut under flight conditions. This bypass, shown in the schematic flow diagram, figure 12, permits 90% of the air containing contaminants from the oven to reach the animal exposure chamber without being altered in composition by the CO₂ scrubbing material. The possibility of using molecular sieve rather than lithium hydroxide for CO₂ removal was evaluated for use in the cabin material toxicity screening program. It was determined that the volume of CO₂ and water vapor produced by metabolism for the number of experimental animals used in these exposures would require replacement or regeneration of the scrubber material approximately four times daily, thus making it an impractical choice for this purpose.

Another modification was the addition of a thin teflon sheet bonded to the bottom of the animal exposure chamber to improve removal of fecal waste. In addition, the flushing system was modified to permit periodic water flushing from outside the Thomas Dome. The flushing has been conducted in subsequent experiments at 4-hour intervals and has significantly improved the removal of animal waste.

Preconditioning Chambers

The preconditioning chambers originally located in the ambient laboratory had to be relocated to make way for building changes related to the addition of the four new Thomas Domes and additional support laboratory space. The chambers were installed, in Building 429, with permanent waste drains and both air supply and exhaust systems. They were returned to service for animal preconditioning in March of 1968.

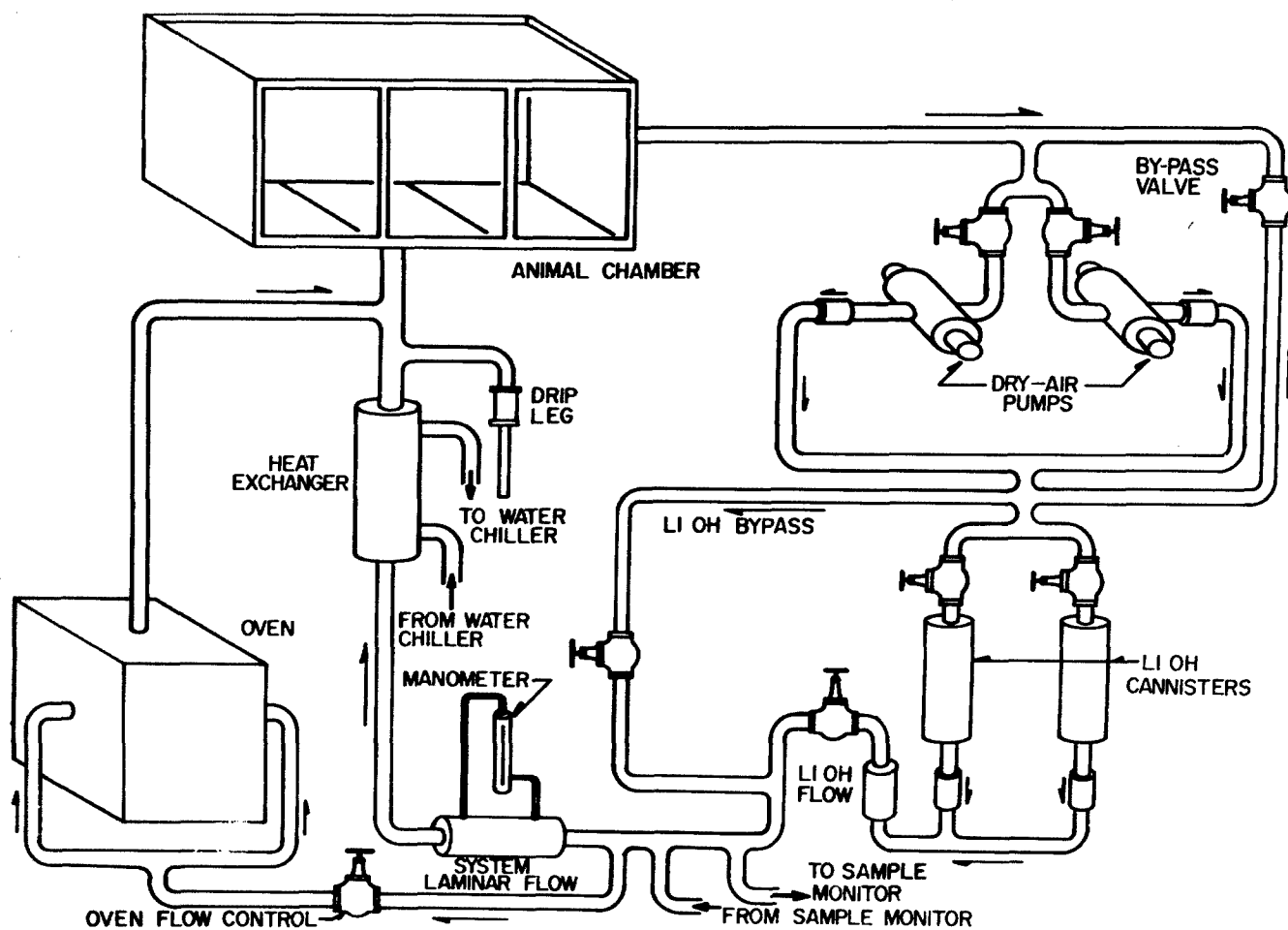


Figure 12. Cabin Materials Screening System Modification

Gas Mixing Valves

The gas blending valves originally installed on the Thomas Domes were operated manually. During the past two years the increased number of experiments conducted with two-gas environments dictated the need for automatic regulation of gas blending. Initial attempts at automatic control were abandoned when it was noted that the atmospheric composition fluctuated greatly around the desired setting. An analysis of the problem revealed the need for a smaller valve designed to operate at a flow rate close to the normal dome flow. These valves have been installed on two domes, successfully controlling the desired mixture within 1%. They allow less excursion of gas composition and permit both significantly faster stabilization and equilibration. The new valves will be installed in the remaining two domes when current experiments are completed.

TRAINING PROGRAMS

Prior to reactivation of the altitude facility of the THRU in December, a training program was initiated to familiarize the chamber technicians and shift engineering technicians with new or revised standard operating procedures. More important was their familiarization with the new emergency operating procedures. This training was a combination of didactic lectures, demonstrations and on-the-job experience. Both written and practical examinations were given to the participating technicians to measure the value of the training program.

An evaluation of the training program resulted in a master plan for continued training on a multi-phasic basis. Phase I of the program was initiated in February 1968. At this time a group of Air Force altitude chamber technicians were included in the program with Systemed technicians. Again the training program included on-the-job experience and a number of Air Force technicians became qualified to operate the Thomas Domes.

The components for a closed-circuit television system were received in January. These components included a video recorder, monitor, camera and other accessories. The first session of the revised training program was taped to investigate the use of this equipment in training programs. Subsequent to the training session, a critique was conducted to evaluate the use of videotaped lectures made under actual conditions. The taped lecture, while slightly imperfect, was sufficiently useful that a decision was made to tape a series of lectures for periodic reuse in refresher training or training of new employees. The need was determined, however, for careful staging of the lectures to assure good quality taped training programs.

SECTION III

RESEARCH PROGRAM

The inhalation toxicology research activities of the THRU were partially curtailed during the first half of the period covered in this report. The Thomas Domes were out of service until December 1967 when restrictions on the use of these chambers for experimentation with oxygen rich environments were lifted for the first modified dome. Upon completion of the new automatic fire extinguishing system in each dome, examination by representatives of the AMD Safety Committee resulted in permission from headquarters AFSC to use the chambers.

Although some research was continued in the ambient facility during the preceding period of dome inactivity, the primary efforts of the THRU staff were directed toward meeting the requirements for getting the domes back into operation at the earliest possible time.

Among the research experiments discussed only three have been completed as of the reporting date. The remaining experiments are continuing and will be described in more detail in ensuing reports. The toxicity screening studies of space cabin construction materials are conducted whenever a sufficient number of materials becomes available for testing.

Monomethylhydrazine

The investigation of monomethylhydrazine (MMH) toxicity has been continued through the current reporting year. Single inhalation exposures of four animal species to MMH for the determination of LC_{50} values (estimated for dogs) were described in the previous annual report (reference 5). A consistent finding in the nonfatal exposure of dogs to concentrations of MMH at or near the approximate LC_{50} value was a transient hemolytic anemia characterized by a significant decrease in hematocrit, red blood cells, and hemoglobin which continued for several days postexposure. The destruction of red blood cells was accompanied by an increase in numbers of reticulocytes during the period of maximum decline of hematocrit levels. The process of recovery was complete within 30 days postexposure at which time normal values of the affected blood parameters were observed. Small groups of *Macaca mulatta* monkeys were exposed to MMH to determine their response relative to the squirrel monkeys previously exposed. On the basis of results from 1-hour exposure periods, and in view of the finding that other species have shown a rather predictable response to a CT (concentration x time) gradient, Rhesus monkeys are apparently more resistant to the acute effects of MMH than either the squirrel monkey or the dog. One-hour exposures to concentrations at or above 170 ppm

of MMH proved lethal, whereas exposures ranging from 120 to 160 ppm did not; this response would seem to place the Rhesus monkey between the rat and the mouse in susceptibility to MMH. An approximate one hour LC_{50} of 162 ppm MMH was determined for this species.

Exposures of Rhesus monkeys to maximal nonlethal concentrations of MMH have rather conclusively shown that the typical hematologic response exhibited by dogs does not obtain for this subhuman primate; there is but slight evidence of the anemia previously described for dogs. This finding is in agreement with data from studies on the effects of injected monomethylhydrazine (reference 9) wherein it has been shown that the monkey responds but slightly insofar as erythrocyte hemolysis is concerned.

A group of three Rhesus monkeys were subjected to repeated inhalation exposures at a 160 ppm concentration of MMH at weekly intervals for four weeks during which time the exposed animals appeared to be developing tolerance to its effects. Initial exposures resulted in emesis and convulsions which were delayed and increasingly less severe in subsequent exposures. The test animals were again exposed on the fifth week to an MMH concentration of 170 ppm, a 10 ppm increase, and at this time two additional Rhesus monkeys were included in the exposure group. The original three animals demonstrated only mild CNS responses, but the two previously unexposed monkeys exhibited severe CNS changes, including convulsions during which one animal died. After a one-month rest period, two of the original group of three Rhesus monkeys received a sixth MMH exposure; this time to a 180 ppm concentration, again with only mild CNS responses. While conclusive evidence of MMH tolerance was not demonstrated, there is some evidence that adaptation of these monkeys had occurred. Hematologic studies of these animals revealed mild to moderate erythrocyte hemolysis (approximately 10% reduction of RBC) with rapid recovery.

The pathologic evaluation of tissues from animals exposed to lethal or near lethal concentrations of MMH is not complete. However, preliminary information on dogs, rats, and squirrel monkeys can be summarized at this time. A common finding in all species, following lethal exposures to MMH, was pulmonary congestion with some hemorrhage, hepatic congestion of varying degree, and swelling of the renal tubular epithelium which was frequently glassine and eosinophilic in appearance. In large animals, whose brain tissues were examined, subarachnoid hemorrhage was frequently observed. This response was probably related to the severe convulsions observed, as was the consistent finding in dogs of remarkably bloodless spleens in which the sinusoids were virtually empty. In some cases, the splenic smooth muscle bundles appeared thickened and contracted.

The amount of visceral congestion and hemorrhage observed was not sufficient to produce death and could only be attributed to CNS damage as previously reported by Jacobson et al (reference 6).

In animals that survived near lethal exposures to MMH and were killed over a period of approximately 60 days postexposure, the visceral congestion was still apparent although not as severe as in those animals that died during exposure. The most common and persistent finding, however, was renal damage which ranged from mild swelling of the tubular epithelium to vacuolization and coagulative necrosis of those epithelial cells.

The primary purpose for the investigation and definition of MMH LC_{50} values was to form some basis for subsequent studies designed to assist in the interpretation of emergency exposure limits (EEL) for man. The basic philosophy pertaining to Short-Term Limits and Emergency Exposure Limits (EEL's) for inhalation of toxic substances has been frequently discussed by others (references 1, 3, and 13) and will not be reiterated here. Very briefly, however, the latter term refers to a "single event" limited exposure which is not expected to incapacitate sufficiently to prevent escape. Such an exposure would be one where the occurrence was possible but unpredictable, and where an individual so exposed would not encounter the substance again until careful study indicated either no injury, or in the event of injury a complete recovery. Emergency inhalation exposures, therefore, are not to be associated with acceptable concentrations in work environment atmosphere.

EEL's currently in use for MMH are 3, 7 and 10 ppm for 60, 30 and 10 minutes, respectively. On the basis of animal response to acute MMH exposures, and in view of the purpose for recommendation of EEL's, it appeared that higher values for MMH might have been warranted. Accordingly, some experimentation was necessary for clarification of this point, and the rationale for such experimentation is given below.

The plot of LC_{50} 's for each of four animal species tested is shown in figure 13. Plots of MMH concentration versus time permit extrapolation of the best fit lines through the respective LC_{50} values and yield a theoretical straight-line dose-response for each species. Thus, from a theoretical viewpoint, two rodent species (rats and mice) exposed continuously to 3.5 - 5 ppm of MMH would exhibit a 50% lethal response following approximately one week of exposure, whereas beagles and squirrel monkeys given this exposure would show 50% response at approximately one day (24 hours). Preliminary experiments with Rhesus monkeys, however, indicated a response midway between that shown for mice and rats. The squirrel monkeys, therefore, represent the most susceptible species tested.

It is well known that the plot of theoretical values cannot be considered as a true dose-response relationship; the reactivity of MMH and the body defense mechanisms undoubtedly negate such an empirical response. Even so, the straight-line plots shown in figure 13 should represent the maximum

LC₅₀ VALUES OF FOUR SPECIES

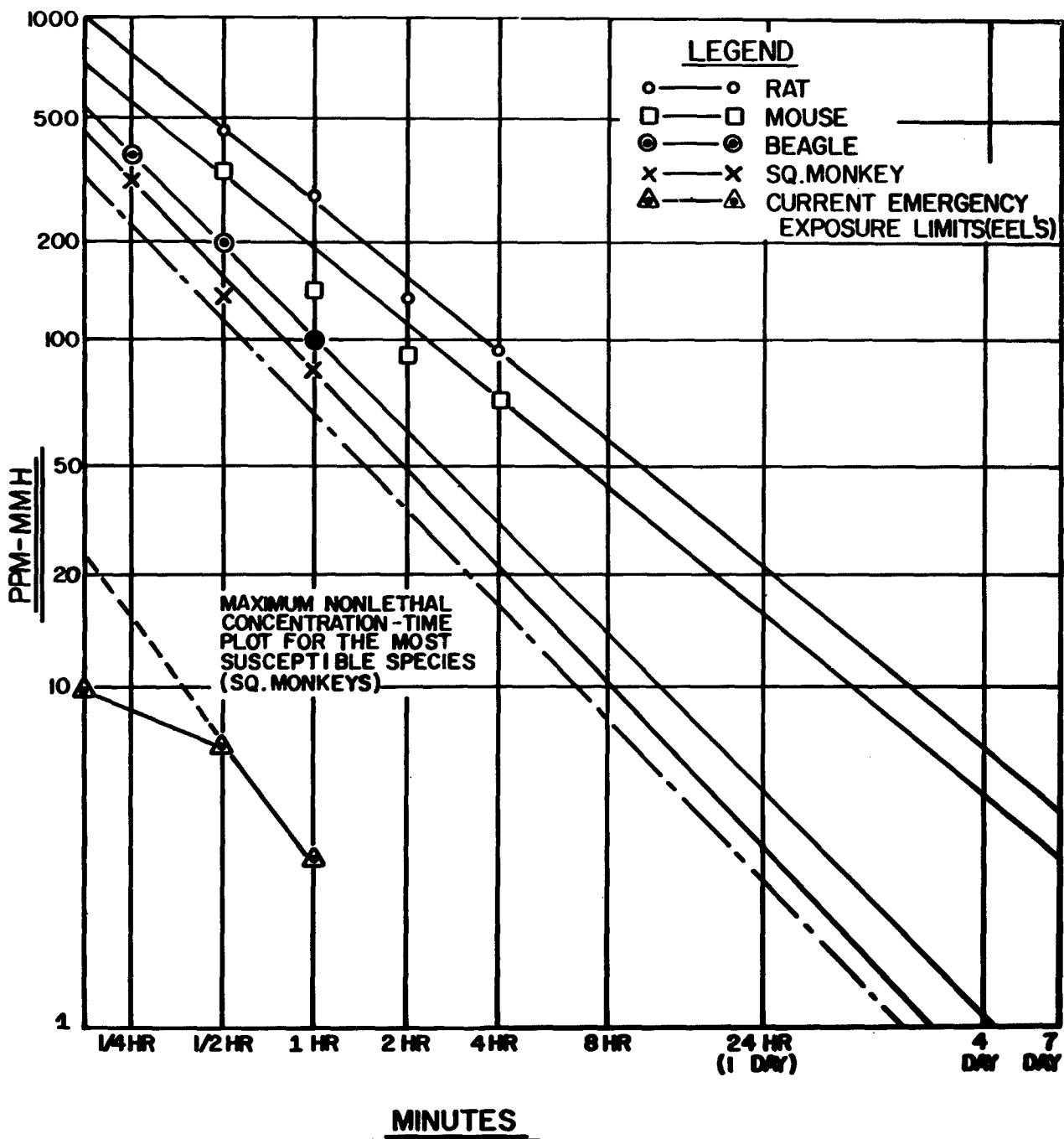


Figure 13. Acute Toxicity of Monomethylhydrazine

possible response; in theory, as well as actuality, response can be expected to wane as the concentration decreases over an increased period of time. For example, the concentration x time (CT) concept will usually hold true within certain limits and then it invariably becomes less meaningful. Typically, an agent which produces morbidity and death at 10 ppm in 1 hour (CT = 10) will also produce an effect at 5 ppm for 2 hours (CT = 10), and perhaps even at 1 ppm for 10 hours (CT = 10); however, the same agent inhaled in a concentration of 0.01 ppm for 1000 hours (CT = 10), or approximately 40 days, will more often than not be innocuous because defense mechanisms "handle" the material prior to production of biochemical lesions. There are exceptions to the rule, of course, since some agents with an accumulative effect may ideally follow an empirical CT concept. Generally speaking, however, it is safe to assume that protracted extensions of LC_{50} plots (as seen in figure 13) represent a theoretical response well above that actually observed.

In this context, then, experiments were designed to indicate the validity of recommended EEL's for MMH. Current EEL's are shown as point plots in figure 13. Note that a straight-line dose-time relationship has not been recommended. If this had been applied, however, the 10-minute EEL would have been set at approximately 30 ppm of MMH rather than the currently suggested 10 ppm.

The MMH concentrations selected for EEL testing on the four selected species (rat, mouse, beagle dog and Rhesus monkey) were based on a CT of 900 ppm minutes. This CT value was approximately 25% of maximum non-lethal concentrations for the most susceptible species, the squirrel monkey, and was also five times higher than the current EEL values adopted by the NAS-NRC Advisory Center on Toxicology. The selected concentrations were 15, 30, and 60 ppm MMH for single exposure periods of 60, 30, and 15 minutes respectively. Rodents and most dogs and monkeys were killed at 1, 3, and 7 days postexposure for necropsy information. A second grouping of two dogs and two monkeys exposed to each MMH time-concentration group were used for pre- and postexposure blood sampling. They were also killed 30 days postexposure and tissue specimens submitted for histopathology to determine reversibility of injury should any such have occurred from the MMH exposures.

Small groups of rodents, both rats and mice, were subjected to higher time-concentration exposures; namely 150, 75, and 40 ppm MMH for 15, 30, and 60 minutes respectively.

No significant differences between MMH exposed and control rodents were observed at any of the six selected EEL test concentrations. This included gross pathology and growth rates for both rats and mice as well as organ to body weight ratios.

No effects on body weight were observed in either dogs or monkeys exposed to three 900 ppm minutes MMH exposure systems. At necropsy mild transitory changes were seen in both species which consisted of minimal congestion with slightly increased pigmentation of the renal cortex. These changes had completely resolved by the 30-day sacrifice period. The results of histopathologic evaluation of tissues from all exposed animals have not been received at the time of this report but will be discussed in a subsequent separate comprehensive technical report on MMH toxicity.

No clinical signs or symptoms of CNS changes could be observed in any of the four animal species exposed to MMH in the EEL test series. There was also no indication of respiratory irritation as had been displayed in MMH concentrations near the LC_{50} range. A statistical review was conducted for those biochemical determinations made on blood specimens taken from both dogs and monkeys exposed to three concentration-time period combinations. The results of the statistical evaluation of the data were consistent at all time levels and in both species showing significant decreases in several of the blood chemistry determinations, some of which appeared to be progressive during the postexposure period. Specifically, decreased values were found in serum potassium, total inorganic phosphorus, blood urea nitrogen, glucose, and although not as consistent, a definite downward trend was observed in sodium levels. These changes were persisting at the time the experiment was terminated and, consequently, a no-effect level had apparently not been reached. Before further experimentation with other MMH concentrations, an additional experiment will be conducted with a slightly larger group of animals at one previously tested concentration to recheck these findings.

Nitrogen Trifluoride

Nitrogen trifluoride (NF_3) toxicity investigations were undertaken to evaluate its acute toxicity to multiple species of animals. These studies are not an end in themselves but are conducted in preparation for further investigations to define suitable NF_3 emergency exposure limits for man. The toxicity studies reported by Torkelson et al (reference 15) were used as the starting point in the THRU investigations.

A gas chromatographic analytical method for monitoring NF_3 exposures was developed which gave 95% confidence limits of $\pm 5\%$ relative. The analytical method uses silica gel for the substrate medium, helium carrier gas, a temperature of 40 C and a manual gas sampling valve to introduce a 4 ml sample. Analyses can be performed every two minutes, sufficient to cover a 15-minute exposure. Technicians were trained to use the procedure and found it very satisfactory in controlling NF_3 concentrations in both large and small animal exposures.

The preliminary results of the not yet completed current series of animal exposures to high concentrations of NF_3 indicate a relatively constant CT (concentration x time) ratio for the four species tested with relatively little difference between species in susceptibility to this strong oxidizing compound.

During exposure to the near lethal concentration of NF_3 , all animals showed signs of mucous membrane and respiratory irritation. Emesis, prostration, and unconsciousness were also occasionally observed. Both increased respiratory rates and tachycardia were observed in dogs and Rhesus monkeys, and rectal temperatures of dogs decreased during the exposure period, persisting for approximately 5-hours after cessation of the exposure. Severe temperature depression has been observed in some animals. These animals generally did not survive the exposure to NF_3 .

As previously reported by Torkelson (reference 15), the inhaled NF_3 reacts with oxyhemoglobin to form methemoglobin. The accompanying anoxia that resulted from low oxyhemoglobin levels was determined to be the cause of death in fatal exposures. A spectrophotometric method of blood examination was developed which permitted the simultaneous determination of blood oxyhemoglobin, methemoglobin, and turbidity using one blood sample at pH 5.5 in an acetate buffer. The technique measures turbidity by absorbance at $720 \text{ m}\mu$, methemoglobin at $630 \text{ m}\mu$ and oxyhemoglobin at $577 \text{ m}\mu$, the latter two being calculated after subtraction of the effects due to the components measured at longer wavelengths. Serial blood sampling of animals exposed to nonfatal concentrations indicated that the NF_3 induced methemoglobin persists in both dogs and monkeys for approximately 24 hours after exposure. The ensuing disappearance of methemoglobin is not, however, accompanied by a return of oxyhemoglobin to preexposure levels. A persistent serum turbidity is observed which may be associated with Heinz body formation. The oxyhemoglobin levels return to preexposure levels, along with the disappearance of serum turbidity by the thirtieth postexposure day. Further investigation of this phenomenon is being conducted concurrently with other studies.

Upon completion of a few remaining planned acute exposures, to clarify the LC_{50} determinations, there will be sufficient data available to design a study for evaluation of NF_3 emergency exposure limits.

Mixed Gas-Reduced Pressure Environments

An 8-month investigation on the effects of continuous exposure to an environment consisting of a 68% O_2 - 32% N_2 gas mixture at 5 psia pressure is currently being conducted. This investigation was undertaken to repeat a previous one in which one species, the dog, exhibited inverted A/G ratios beginning during the third month of exposure and continuing until the experiment was completed. The purpose of the current investigation is to verify

that the previously observed changes and trends were actually the result of exposure to the mixed gas environmental conditions. Consequently, all dogs selected both for the dome exposure and as controls had high normal A/G ratios which had been measured repetitively during the preexposure period.

During the third month of exposure occasional test dogs demonstrated inverted A/G ratios. These inversions of ratios have not repeated and after five months of continuous exposure there are no apparent differences between the control and the exposed dogs. Exposed male rats, however, have exhibited a depressed growth rate which has been significant at the 1% level. This trend was seen in the previous experiment although it was not statistically significant. The experiment is continuing.

Dome Exposure of Control Animals

The use of control animals housed in Thomas Domes had proven to be unnecessary for short term or acute toxicity experiments but had not previously been investigated for long duration experiments. The period of dome inactivity, while experimentation with oxygen enriched environments was curtailed, presented an opportunity to evaluate the effect of the inherent dome operating conditions on control animals. The purpose of the investigation was to determine whether animal room housed control animals were acceptable for comparison with animals exposed to contaminants in the domes for prolonged periods or whether it was necessary to house control animals in another dome. The dome environmental conditions different from those encountered in the animal room were (1) reduced ventilation exchange rates, (2) elevated noise levels, (3) uniform temperature and relative humidity, (4) increased odor levels and (5) housing of four different animal species in close proximity.

The data resulting from this experiment is currently under evaluation for preparation of a separate technical report and for presentation at the 4th Annual Conference on Atmospheric Contamination in Confined Spaces. A preliminary review of the data indicates the differences between the dome housed rodents and their animal room controls were not great and the changes observed in primates and dogs appeared to represent a possible trend toward general improvement of health status. The clinical measurements increased slightly from low "normal" ranges (references 10 and 11) to mid "normal" ranges and also became more stable. The answer to the postulated question, "Are dome controls necessary?", awaits final evaluation of the amassed data.

Investigation of Harvest Technique on Organ Weights

The versatility of experimental toxicologic methodologies available in the THRU with altitude chambers as well as standard inhalation exposure facilities has created a small quandary concerning the most suitable euthanasia

technique when animal organ weight data are to be collected and used as indices of biological stress. When animals are individually housed and kept in ambient pressure facilities, there are no serious problems encountered in conducting overnight fasting or other special treatment of selected animals before killing them. In the Thomas Domes, however, such special procedures are more difficult to carry out. This investigation was undertaken to determine whether special treatment led to sufficiently increased data precision to merit its use.

For several years, pharmacologists and toxicologists have utilized organ weight as a tool in determining the relative toxicity of various compounds. The basic assumption underlying this approach concerns itself with the reaction of tissues to chemical or drug insult. Subtle organ modifications may result in mild edema or slight cellular proliferation. However, these subtle modifications are not always histologically detectable but produce measurable changes in total organ weight. If organ weight modifications do occur, it is important to be certain that they are due to chemical insult and not to the sacrifice technique. The latter can easily mask changes induced by the experimental insult. Highly vascularized organs can display marked weight variations in response to the influence of barbiturates because of blanching or engorgment of the organ's vascular system. Also, organs associated with the digestive function, such as the liver, may reflect weight changes resulting from presacrifice diet habits. Therefore, it was decided to examine the effect of overnight fasting versus feeding, and exsanguination versus barbiturate overdose on the organ weight variation. A total of four combinations of diet and euthanasia technique were selected: exsanguinated-fasted, exsanguinated-fed, barbiturate overdosage-fasted, barbiturate overdosage-fed.

Sprague Dawley strain, male Charles River rats, 80-100 grams, were used in all phases of the experiment. All rats were fed ad libitum, and caged so as to allow for uninhibited body growth. The experiment was carried out in two phases:

Phase I

Rats were randomly grouped into 40 sets of 7 rats each, with 4 sets killed each week for 10 weeks in one of the following manners:

1. Deprived of food for 12 hours and killed with Uthol*.
2. Fed ad libitum prior to euthanasia with Uthol*.
3. Deprived of food for 12 hours and killed by exsanguination.
4. Fed ad libitum prior to euthanasia by exsanguination.

All rats were weighed each week. Gross pathology and organ weights were recorded for all animals submitted for necropsy.

*Trade Name

Phase II

Rats were randomly grouped into 30 sets consisting of 10 rats each. One set was killed each week until all the groups had been used. Animals in this phase were fasted for 12 hours before euthanasia by exsanguination.

Uthol treatment was accomplished with an intraperitoneal injection. Prior to exsanguination, rats were anesthetized with an injection of pentobarbital sodium. Exsanguination was accomplished by cutting through the femoral artery and vein bilaterally.

The evaluation of the data collected during this experiment is incomplete; however, tests of minimum error indicate that the rats that were fasted overnight and euthanized by exsanguination gave results which were the most uniform. The data evaluation will be completed in the near future and will also be presented at the 4th Annual Conference on Atmospheric Contamination in Confined Spaces.

Toxicity Screening-Space Cabin Materials

A continuing program of toxicity screening of space cabin construction materials is conducted for both Air Force and NASA space flight systems. As materials are received for screening, they are assembled into groups of 15 to 20 and prepared, if necessary, according to manufacturers directions. The preparations include painting shellacs, varnishes, and other surface coating materials on metal foil, and mixing and curing plastic polymer formulations.

The prepared group of materials is placed in a vacuum oven which is part of the closed loop life support system previously described (reference 5). The oven is heated to 155 F at 5 psia and then the breathing atmosphere is passed through the oven and introduced into the animal exposure portion of the closed loop with the added gas-off products.

Three variations in the experimental protocol followed in the screening procedure have been introduced during the past year. Originally the cabin materials placed in the oven were scaled in weight relative to the amount used in an actual space vehicle cabin. The procedure followed for 7-day exposures was to use 10 grams when less than one pound was in actual use and 100 grams when usage exceeded one pound. Since actual use quantities of the great variety of materials needed was difficult to ascertain, the program was modified to test 100 grams amounts of all materials used in NASA flight systems. For 60-day experiments, a standard amount of 10 grams of each material is used. The decreased amounts used for 60-day experiments is to allow larger numbers (up to 100 compounds) of materials to be tested.

The second change was to necropsy the experimental animals in two groups at two and four weeks postexposure rather than at weekly intervals for four periods. This change resulted in animal group sizes which were more useful for statistical evaluation of growth rates and organ to body weight ratios.

Finally, a bypass loop around the lithium hydroxide canister in the life support system permitted operation at CO₂ concentrations more comparable to actual space flight conditions. The bypass system also decreases the possibility of the test contaminant being adsorbed on the lithium hydroxide, thereby reducing the concentration to which animals are exposed.

Since resumption of experimentation, four groups of materials have been screened for toxicity. Groups I and II of cabin materials were investigated in the newly constructed systems in Dome 1. Because this was the first test run in this system, a replicate experiment was included in the test protocol. During the first run some mortality occurred in mice exposed to Group II materials, and some operational problems were also encountered in the life support system. The problems were corrected before the second run, and during this run no differences were observed between the animals exposed to Groups I and II materials and their positive controls housed in the third life support loop.

The investigation of potential toxicity of Groups N and O has not been completed as of the time of this report.

Carboxy Nitroso Rubber

Carboxy nitroso rubber (CNR) is a synthetic polymer with rubber-like properties and has the added property of being noncombustible. Due to its noncombustible property CNR was selected as a candidate material for use in spacecraft cabins as a replacement for combustible materials with similar properties of softness and stretch.

Carboxy nitroso rubber was first submitted to the THRU for determination of flammability in 100% oxygen and for chemical analysis of any pyrolysis products formed. Insofar as can be determined from information supplied by the manufacturer, the formulation of CNR is:

	<u>Compound</u>	<u>Formula</u>	<u>Weight %</u>	
CNR gum	Nitrosotrifluoromethane	CF_3NO	?	} 80
	Perfluoroethylene	C_2F_4	?	
	Perfluoronitrosobutyric acid	$\text{HOOC}(\text{CF}_2)_3\text{NO}$	2	
	Silstone 110 (10% Silicone oil coated silica)	SiO_2 $(\text{R}_2\text{Si}-\text{O})_n$	14.4 1.6	} 16
	Chromium trifluoroacetate	$\text{CrOOC}(\text{CF}_3)_2$		
				4

A portion of CNR was placed in a small chamber filled with oxygen at ambient pressure. Ignition was attempted using a nichrome resistance wire heated to 800 C. No burning occurred; instead the wire melted through the rubber releasing visible, acrid fumes.

One gram of CNR was pyrolyzed in a glass stoppered 250 ml flask filled with 100% oxygen. The flask was slowly heated, using a low flame, until the beginning of reaction, signalled by physical decomposition of the rubber into a frothy gray powder and the evolution of dense white fumes. The reaction continued spontaneously for about a minute after initiation. It is estimated that the temperature necessary to initiate pyrolysis was no higher than 300 C.

After cooling, the flask was connected to the batch inlet system of a mass spectrometer, and a pressure of 100 millitorr allowed into the expansion volume. The sample was permitted to diffuse through the 16-hole molecular leak inlet, and mass spectra were recorded immediately and after 30 minutes. Because different molecular sizes have different leak rates, it is often possible to pinpoint different compounds by the ratios of the initial peaks to the 1/2 hour peaks. In addition, the reaction flask was partially evacuated and the remaining vapors reexpanded into the batch inlet system. When this was done, most of the peaks disappeared leaving major peaks at mass number 85 (with isotope peaks at 86 and 87) and 44. Mass number 44 was identified as CO_2 . Mass numbers 85, 86, and 87 were attributed to silicon tetrafluoride (SiF_4) and confirmed by comparison with a literature spectrum of SiF_4 in the API tables as shown in table III.

Table III

Comparison of Unknown Pyrolysis Spectrum with SiF₄

<u>Mass No.</u>	<u>Relative Abundance</u>	
	<u>API SiF₄</u>	<u>Pyrolysis Spectrum</u>
85	100	100
86	5.15	5.23
87	3.44	3.40
104	1.48	2.75

The peaks at mass numbers 86 and 87 are due to silicon isotopes 29 and 30 and represent the abundance of these in nature.

Table IV summarizes the results obtained on the samples allowed to leak into the mass spectrometer from the batch inlet system for 30 minutes, and lists the ratios of the initial to 1/2-hour peaks under the formulas of the compounds assigned to these peaks.

Table IV

Identification of Pyrolysis Products Using Mass Spectrometer Leak Rate

<u>Mass No.</u>	<u>Ratio of Initial Peak Height to 1/2 Hour Peak Height</u>		
	<u>COF₂</u>	<u>CF₃NCO</u>	<u>CF₃CF = NF</u>
47	2.47		
64			1.96
66	2.82		
69		2.95	2.95
92		1.75	
111		1.81	
114			1.90
133			1.90

It can be seen that the ratios are much higher for the peaks at mass numbers 47 and 66. This is to be expected for a low molecular weight compound which will diffuse through the molecular leak much more rapidly than the larger compounds. Mass number 69 shows a high rate of decrease with time because it is a fragment of both CF₃NCO and CF₃CF = NF and would diffuse through the leak with both these compounds.

The pyrolysis products of CNR can, therefore, be summarized as in table V.

Table V

Pyrolysis Products of CNR Identified by Mass Spectrometry

Carbon dioxide	CO_2
Silicon tetrafluoride	SiF_4
Perfluoroethyleneimine	$\text{CF}_3\text{CF} = \text{NF}$
Carbonyl fluoride	COF_2
Trifluoromethyl isocyanate	CF_3NCO

These are listed in the approximate order of their concentration in the pyrolyzate vapors, although no attempt was made to achieve quantitative estimates. It must also be emphasized that these identifications are made solely on the basis of mass spectrometric examination and cannot, therefore, be regarded as unambiguous. However, formation of these compounds appears to be plausible given the formulation of the carboxy nitroso rubber.

Infrared spectra were obtained on the rubber before and after pyrolysis. The prepyrolysis spectrum was obtained using the multiple internal reflectance accessory and the postpyrolysis spectrum by transmittance using a Nujol mull. The main point of interest was the essential disappearance in the spectrum of the pyrolyzed material of bands due to nitroso, carboxy and silica groups, indicating that these had largely reacted and escaped in the vapor. Retained were absorption bands due to C-F and CrO groups which indicated that the chromium remained nonvolatile and that the pyrolysis residue was still highly fluorinated.

One might expect a vapor containing the substances listed in table V to be irritating to the mucous membrane and the whole respiratory system. In truth, one sniff of the pyrolyzate vapor did produce irritation of the nasal passages and bronchial tubes in one experimenter. In view of the observed irritative property of the CNR pyrolyzate, animal experimentation was conducted to define the acute toxicity of the pyrolyzate.

Based on information that approximately 65 grams of CNR would be used in a space cabin having a free volume of 8.3 M^3 an inhalation exposure concentration of 7.65 mg/l was selected for testing. A group of five rats was placed in a thirty-liter chamber which was then purged with O_2 until a 100% O_2 environment was achieved. A sample of CNR placed in a nichrome wire basket was heated to 300°C at which temperature it pyrolyzed and dense white fumes filled the static chamber in which the rats were caged. Four of the five rats died during the 30-minute exposure period and the last animal expired immediately upon removal to ambient air.

During exposure the animals displayed signs of extreme pulmonary eye irritation. Profuse lacrimation and sniffing was followed by prostration during which diaphragmatic breathing was observed. Gross examination of the tissues of the animals showed a uniform picture of massive pulmonary hemorrhage and edema.

A series of experiments were conducted to find the "no-effect" concentration for albino rats exposed to CNR pyrolysis products for 30-minute and 2-minute periods. During 30-minute exposures a concentration of CNR pyrolyzate as low as 0.37 mg/l produced in excess of 80% mortality. A concentration was ultimately reached, 0.20 mg CNR pyrolyzate/l, that did not result in fatalities and further, produced only minimal signs of pulmonary and eye irritation. The lowest concentration producing mortality during 2-minute exposures was determined to be 1.80 mg CNR/l. This value is less accurate than the 30-minute concentration value due to the inherent problems associated with complete termination of animal exposure in 2-minute duration experiments.

Inhalation exposure concentrations selected for testing the "no-effect" level for 2-minute and 30-minute exposures to CNR pyrolyzate were 0.66 mg/l and 0.20 mg/l respectively. Twenty-five male rats were exposed to each concentration time period, during which only occasional animals displayed signs of mild irritation such as blinking or sniffing. The exposed animals were serially killed, as were both positive and animal room controls, over a 14-day postexposure period. All animals were weighed at each necropsy period and then their organs were weighed and submitted for histopathological evaluation.

At the time-concentrations tested the CNR pyrolyzate did not produce any effect on rat growth rate or upon organ to body weight ratios. There were also no apparent gross pathologic differences between the exposed groups of rats and their sham exposed or animal room controls. The histopathologic evaluation of the selected tissue specimens has, however, not been completed as of this reporting date.

The observed toxic response to CNR pyrolyzate cannot readily be explained with respect to a specific causative agent. With the exception of perfluoroethyleneimine, none of the compounds identified in the CNR pyrolyzate, listed in table V, have been reported to be as highly toxic as was observed. A preliminary search of the literature has not revealed any information on the toxicity of perfluoroethyleneimine. If a molecular weight of 100 is assumed for the responsible agent then a concentration of 450 ppm breathed for a 2-minute period is lethal and a concentration of less than 100 ppm inhaled for a 30-minute period would prove fatal. This highly toxic material would represent a serious hazard to housewives and to firefighters if it is found to have domestic or commercial application.

Planned Research

Research plans for the ensuing report period include the completion of on-going research. Monomethylhydrazine investigations will be expanded and chronic toxicity experiments will be conducted. These investigations will be coordinated with other research groups so that maximum information can be obtained, especially with respect to the examination of kidney function and related histologic approaches.

Nitrogen trifluoride investigations will be extended to include the definition of safe emergency exposure limits. A similar but more reactive oxidizing compound, ClF_3 , will be investigated and data will be evaluated to define emergency limits.

Further experiments on the ocular effects of continuous exposure to ethylene glycol will also be conducted. Four additional Thomas Domes will be made available for experimentation and problems associated with exposure limits for 100- and 1000-day space flight missions will be investigated in these chambers.

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DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author) SysteMed Corporation Overlook Branch, P. O. Box 3067 Dayton, Ohio 45431		2a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	
		2b. GROUP N/A	
3. REPORT TITLE TOXIC HAZARDS RESEARCH UNIT ANNUAL TECHNICAL REPORT: 1968			
4. DESCRIPTIVE NOTES (Type of report and inclusive dates) Final Report, September 1967 - May 1968			
5. AUTHOR(S) (First name, middle initial, last name) J. D. MacEwen and E. H. Vernot			
6. REPORT DATE October 1968	7a. TOTAL NO. OF PAGES 49	7b. NO. OF REFS 15	
8a. CONTRACT OR GRANT NO. F33615-67-C-1025		9a. ORIGINATOR'S REPORT NUMBER(S) SysteMed Report No. W-68001	
b. PROJECT NO. 6302			
c. Task No. 630201		9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report) AMRL-TR-68-133	
d.			
10. DISTRIBUTION STATEMENT This document has been approved for public release and sale; its distribution is unlimited.			
11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Aerospace Medical Research Laboratories, Aerospace Medical Div., Air Force Systems Command, Wright-Patterson AFB, OH 45433	
13. ABSTRACT The activities of the Toxic Hazards Research Unit (THRU) for the period of September 1967 through May 1968 are reviewed in this report. The experimental research program was partially curtailed during the first half of this period while major modifications to the Thomas Domes of the Altitude Facility were being completed. The dome modifications, primarily for improved fire safety protection, were required to be complete before experimentation in oxygen enriched environments could be resumed. Additional facilities for toxicity screening of space cabin materials were placed in service and the evaluation of materials has been continued with little evidence of toxicity exhibited by their gas-off products. One cabin material, carboxy nitroso rubber (CNR), did exhibit toxic manifestations and its acute toxic effects were investigated in depth. The CNR pyrolysis products formed at 300 C were found to be highly toxic and any human exposure to these products should be guarded against. Acute toxicity experiments on monomethylhydrazine and nitrogen trifluoride, including MMH emergency tolerance limits studies were conducted in the Ambient Facilities of the THRU. Investigations on the use of sham exposed dome controls and techniques for determining organ to body weight ratios are reported.			

14.	KEY WORDS	LINK A		LINK B		LINK C	
		ROLE	WT	ROLE	WT	ROLE	WT
	Toxicology Thomas Domes Instrumentation Medical Research Atmosphere Monitoring Space Cabin Toxicology Materials Testing						